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Search Notes

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FILE COVERS 1907 - 30 Nov 2005  VOL 143 ISS 23
FILE LAST UPDATED: 29 Nov 2005  (20051129/ED)

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FILE COVERS 1907 - 30 Nov 2005  VOL 143 ISS 23
FILE LAST UPDATED: 29 Nov 2005  (20051129/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

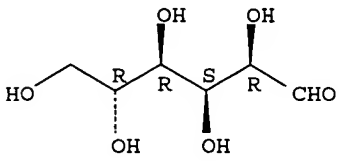
=> d all hitstr l140 tot

L140 ANSWER 1 OF 11  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   2005:476684  HCAPLUS
DN   143:206173
ED   Entered STN:  06 Jun 2005
TI   Inhibition of dipeptidyl peptidase IV activity by oral
     metformin in type 2 diabetes
AU   Lindsay, J. R.; Duffy, N. A.; McKillop, A. M.; Ardill, J.; O'Harte, F. P.
     M.; Flatt, P. R.; Bell, P. M.
CS   Regional Centre for Endocrinology and Diabetes, Royal Victoria Hospital,
     University of Ulster, Coleraine, UK
SO   Diabetic Medicine (2005), 22(5), 654-657
     CODEN: DIMEEV; ISSN: 0742-3071
PB   Blackwell Publishing Ltd.
DT   Journal
```

LA English
CC 1-10 (Pharmacology)
AB Glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) are important insulinotropic hormones that enhance the insulin secretory response to feeding. Their potential for treating Type 2 diabetes is limited by short biol. half-life owing to degradation by **dipeptidyl peptidase** IV (**DPP IV**). We investigated the acute effects of **metformin** on **DPP IV** activity in Type 2 diabetes to elucidate inhibition of **DPP IV** as a possible mechanism of action. Eight fasting subjects with Type 2 diabetes (5M/3F, age 53.1±4.2 years, BMI 36.8±1.8 kg/m2, glucose 8.9±1.2 mmol/l, HbA1c 7.8±0.6%) received placebo or **metformin** 1 g orally 1 wk apart in a random, crossover design. Following **metformin**, **DPP IV** activity was suppressed compared with placebo (AUC0-6 h 3230±373 vs. 5764±504 nmol ml/l, resp., P = 0.001). Circulating glucose, insulin and total GLP-1 were unchanged. **Metformin** also concentration-dependently inhibited endogenous **DPP IV** activity in vitro in plasma from Type 2 diabetic subjects. Oral **metformin** effectively inhibits **DPP IV** activity in Type 2 diabetic patients, suggesting that the drug may have potential for future combination therapy with incretin hormones.
ST **metformin dipeptidyl peptidaseIV** inhibitor type2 diabetes
IT Human
(inhibition of **dipeptidyl peptidase** IV activity by oral **metformin** in type 2 diabetes)
IT **Diabetes mellitus**
(**non-insulin-dependent**; inhibition of **dipeptidyl peptidase** IV activity by oral **metformin** in type 2 diabetes)
IT **Antidiabetic agents**
(**oral**; inhibition of **dipeptidyl peptidase** IV activity by **oral metformin** in type 2 diabetes)
IT **50-99-7**, D-Glucose, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**blood**; inhibition of **dipeptidyl peptidase** IV activity by oral **metformin** in type 2 diabetes)
IT 9004-10-8, Insulin, biological studies **54249-88-6**, **Dipeptidyl peptidase** IV 89750-14-1, Glucagon-like peptide-1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition of **dipeptidyl peptidase** IV activity by oral **metformin** in type 2 diabetes)
IT **657-24-9**, **Metformin**
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(inhibition of **dipeptidyl peptidase** IV activity by oral **metformin** in type 2 diabetes)
RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Bell, P; Endocrinol Metab Clin North Am 1997, V26, P523 HCAPLUS
(2) Drucker, D; Expert Opin Invest Drugs 2003, V12, P87 HCAPLUS
(3) Fujiwara, K; J Biochem 1978, V83, P1145 HCAPLUS
(4) Hinke, S; Biochem Biophys Res Commun 2002, V291, P1302 HCAPLUS
(5) Knowler, W; N Engl J Med 2002, V346, P393 HCAPLUS
(6) Mannucci, E; Diabetes Care 2001, V24, P489 HCAPLUS
(7) Meier, J; Biodrugs 2003, V17, P93 HCAPLUS
(8) Mentlein, R; Eur J Biochem 1993, V214, P829 HCAPLUS
(9) O'Harte, F; Diabetologia 2002, V45, P1281 HCAPLUS
(10) Sudre, B; Diabetes 2002, V51, P1461 HCAPLUS
(11) Yasuda, N; Biochem Biophy Res Commun 2002, V298, P779 HCAPLUS
(12) Zander, M; Diabetes Care 2001, V24, P720 HCAPLUS
(13) Zarghi, A; J Pharmaceut Biomed Anal 2002, V31, P197
IT **50-99-7**, D-Glucose, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)

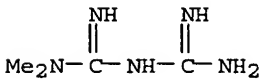
(**blood**; inhibition of **dipeptidyl peptidase** IV activity by oral **metformin** in type 2 diabetes)
RN 50-99-7 HCAPLUS
CN D-Glucose (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **54249-88-6, Dipeptidyl peptidase** IV
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition of **dipeptidyl peptidase** IV activity by oral **metformin** in type 2 diabetes)
RN 54249-88-6 HCAPLUS
CN Peptidase, dipeptidyl, IV (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **657-24-9, Metformin**
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(inhibition of **dipeptidyl peptidase** IV activity by oral **metformin** in type 2 diabetes)
RN 657-24-9 HCAPLUS
CN Imidodicarbonimidic diamide, N,N-dimethyl- (9CI) (CA INDEX NAME)



L140 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2005:216666 HCAPLUS
DN 142:291400
ED Entered STN: 11 Mar 2005
TI Glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control
IN **Demuth, Hans-Ulrich**; Glund, Konrad; Hoffmann, Matthias
PA **Prosidion** Ltd., UK
SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-40
ICS A61K031-426; A61K045-06; A61P003-10
CC 1-10 (Pharmacology)
Section cross-reference(s): 27, 34
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2005020983	A2	20050310	WO 2004-IB3082	20040902 <--
WO 2005020983	A3	20050728		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,

AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2003-499535P P 20030902 <--

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2005020983	ICM	A61K031-40
	ICS	A61K031-426; A61K045-06; A61P003-10
WO 2005020983	ECLA	A61K031/40+M; A61K031/426+M; A61K045/06 <--

AB The invention relates to method of treatment, in particular to a method for the treatment of diabetes mellitus, especially non-insulin dependent diabetes mellitus (NIDDM) or Type 2 diabetes and conditions associated with diabetes mellitus the pre-diabetic state and/or obesity and to compns. for use in such method. The invention comprises the administration of glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other **antidiabetic** agents. Glutaminyl pyrrolidine free base and hydrochloride and glutaminyl thiazolidine hydrochloride were synthesized.

ST glutaminyl thiazolidine hypoglycemic combination glycemia; NIDDM **antidiabetic** combination glutaminyl pyrrolidine; diabetes mellitus glutaminyl thiazolidine prepn; obesity glutaminyl pyrrolidine prepn

IT **Hyperglycemia**
(control of; glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)

IT **Antidiabetic agents**
Antiobesity agents
Combination chemotherapy
Drug metabolism
Human
Obesity
(glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)

IT Drug delivery systems
(injections, intra-arterial; glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)

IT **Diabetes mellitus**
(**non-insulin-dependent**; glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)

IT Enzyme kinetics
(of inhibition; glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)

IT Drug delivery systems
(oral; glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)

IT **Diabetes mellitus**
(pre-diabetic; glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)

IT Blood plasma
(stability of glutaminyl pyrrolidine or glutaminyl thiazolidine in; glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)

IT Peroxisome proliferator-activated receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ, agonist, insulin sensitizer; glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)

IT 9025-32-5, Prolidase 600156-84-1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)

IT 251571-74-1
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)

IT 251571-75-2P
RL: PAC (Pharmacological activity); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)

IT **657-24-9, Metformin** 10238-21-8, Glibenclamide
56180-94-0, Acarbose 122320-73-4, Rosiglitazone
RL: PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)

IT 251571-85-4P 251572-82-4P 482372-57-6P 847545-15-7P 847545-16-8P
847545-17-9P 847545-18-0P 847545-19-1P
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)

IT 109-02-4, 4-Methylmorpholine 123-75-1, Pyrrolidine, reactions
123-91-1, Dioxan, reactions 543-27-1, Isobutylchloroformate 2650-64-8, N-Benzyloxycarbonylglutamine 13726-85-7 14446-47-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)

IT 482372-58-7P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)

IT 56-03-1, Biguanide 64-77-7, Tolbutamide 94-20-2, Chlorpropamide
114-86-3, Phenformin 339-43-5, Carbutamide 631-27-6, Glyclopyramide **692-13-7, Buformin** 968-81-0, Acetohexamide 1156-19-0, Tolazamide 21187-98-4, Gliclazide 24477-37-0, Glisolamide 25046-79-1, Glisoxepide 26944-48-9, Glibornuride 29094-61-9, Glipizide 32797-92-5, Glisentide 33342-05-1, Gliquidone 72432-03-2, Miglitol 74772-77-3, Ciglitazone 80879-63-6, Emiglitate 83480-29-9, Voglibose 93479-97-1, Glimepiride 97322-87-7, Troglitazone 105816-04-4, Nateglinide 109229-58-5, Englitazone 111025-46-8, Pioglitazone 135062-02-1, Repaglinide
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)

IT **50-99-7**, Glucose, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(impaired tolerance; glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)

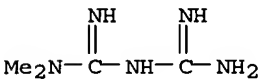
IT 9032-68-2, **Dipeptidyl peptidase I 54249-88-6**, **Dipeptidyl peptidase** IV 72162-84-6, Prolyl oligopeptidase 76199-23-0, **Dipeptidyl peptidase II**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition; glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)

IT 9001-42-7, α-Glucosidase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)

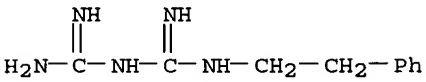
IT 9004-10-8, Insulin, biological studies
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(secretagogue or sensitizer; glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)

IT **657-24-9, Metformin**
RL: PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL

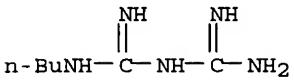
(Biological study); USES (Uses)
(glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)
RN 657-24-9 HCAPLUS
CN Imidodicarbonimidic diamide, N,N-dimethyl- (9CI) (CA INDEX NAME)



IT **114-86-3, Phenformin 692-13-7, Buformin**
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)
RN 114-86-3 HCAPLUS
CN Imidodicarbonimidic diamide, N-(2-phenylethyl)- (9CI) (CA INDEX NAME)

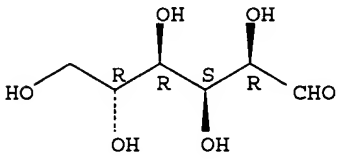


RN 692-13-7 HCAPLUS
CN Imidodicarbonimidic diamide, N-butyl- (9CI) (CA INDEX NAME)



IT **50-99-7**, Glucose, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(impaired tolerance; glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)
RN 50-99-7 HCAPLUS
CN D-Glucose (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **54249-88-6, Dipeptidyl peptidase IV**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition; glutaminyl thiazolidine or glutaminyl pyrrolidine in combination with other hypoglycemic agents for glycemic control)
RN 54249-88-6 HCAPLUS
CN Peptidase, dipeptidyl, IV (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L140 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2005:177846** HCAPLUS
DN 142:254622
ED Entered STN: 03 Mar 2005
TI Compounds and compositions for the treatment of diabetes and

diabetes-related disorders
IN Wang, Yamin; Natero, Reina
PA Bayer Pharmaceuticals Corporation, USA
SO PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC 1-10 (Pharmacology)
Section cross-reference(s): 2, 28
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2005018567	A2	20050303	WO 2004-US27200	20040820
WO 2005018567	A3	20050929		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2003-497109P P 20030822
CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2005018567	ICM	A61K

OS MARPAT 142:254622
AB The present invention relates to novel compds. which are useful in the treatment of diabetes and diabetes-related disorders. The invention also relates to pharmaceutical compns. comprising said compds., intermediates useful in the preparation of said compds., and methods of preparation
ST diabetes treatment compd
IT Pituitary adenylate cyclase-activating polypeptide receptor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(agonists; compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)
IT Drug delivery systems
(carriers; compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)
IT Antidiabetic agents
Antihypertensives
Antiobesity agents
Combination chemotherapy
Diabetes mellitus
Human
Hyperglycemia
Hypertriglyceridemia
Hypolipemic agents
(compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)
IT Sulfonylureas
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)

IT Drug toxicity
Pheochromocytoma
(diabetes from; compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)

IT Lipids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(dyslipidemia; compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)

IT Glucocorticoids
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(excess, diabetes from; compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)

IT Drug delivery systems
(excipients; compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)

IT Pregnancy
(gestational diabetes mellitus; compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)

IT Diabetes mellitus
(gestational; compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)

IT Autoimmune disease
(insulin-dependent diabetes mellitus; compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)

IT Diabetes mellitus
(insulin-dependent; compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)

IT Peroxisome proliferator-activated receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ligands; compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)

IT Disease, animal
(metabolic syndrome X; compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)

IT Diabetes mellitus
(non-insulin-dependent; compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)

IT 9004-10-8, Insulin, biological studies
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)

IT 846576-54-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)

IT 56-03-1D, Biguanide, derivs. 94-20-2, Chloropropamide 1393-25-5, Secretin 1393-25-5D, Secretin, derivs. 9004-10-8D, Insulin, derivs. 10238-21-8, Glibenclamide 29094-61-9, Glipizide 54870-28-9, Meglitinide 59392-49-3, GIP 59392-49-3D, GIP, derivs. **89750-14-1, Glucagon-like peptide-1** **89750-14-1D, Glucagon-like peptide** -1, derivs. 93479-97-1, Glimepiride 105816-04-4, Nateglinide 135062-02-1, Repaglinide 137061-48-4 137061-48-4D, derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)

IT 62-53-3, Aniline, reactions 75-35-4, Vinylidene chloride, reactions 57248-14-3, 2,5-Dichloro-3-thiophenecarbonyl chloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)

IT 846576-52-1P 846576-53-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)

IT 9002-72-6, Growth hormone
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(excess, diabetes from; compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)

IT 50-99-7, Glucose, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(impaired fasting levels and tolerance; compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)

IT 9001-42-7, α-Glucosidase 9041-46-7, 11-β-Hydroxysteroid dehydrogenase 39433-97-1, 11-β-Hydroxysteroid dehydrogenase **54249-88-6, Dipeptidyl peptidase** IV 56941-20-9, 11-β-Hydroxysteroid dehydrogenase 300865-11-6, Protein tyrosine phosphatase-1B
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)

IT **89750-14-1, Glucagon-like peptide-1** **89750-14-1D, Glucagon-like peptide** -1, derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)

RN 89750-14-1 HCAPLUS
CN Glucagon-like peptide I (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 89750-14-1 HCAPLUS
CN Glucagon-like peptide I (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **54249-88-6, Dipeptidyl peptidase IV**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; compds. and compns. for treatment of diabetes and diabetes-related disorders and combination with other agents in relation to treating **secondary** causes and stimulation of insulin secretion)
RN 54249-88-6 HCAPLUS
CN Peptidase, dipeptidyl, IV (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

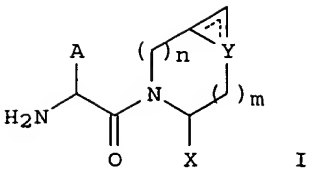
L140 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2005:120884** HCAPLUS
DN **142:219555**
ED Entered STN: 11 Feb 2005
TI Preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV
IN Hamann, Lawrence G.; Khanna, Ashish; Kirby, Mark S.; Magnin, David R.; Simpkins, Ligaya M.; Sutton, James C.; Robl, Jeffrey
PA Bristol-Myers Squibb Company, USA
SO PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D213-00
CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 2005012249	A2	20050210	WO 2004-US24257	20040728	<--
	WO 2005012249	A3	20050506			
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
	US 2005038020	A1	20050217	US 2004-899641	20040727	<--
	US 2005228021	A1	20051013	US 2005-149414	20050609	<--
	US 2005239839	A1	20051027	US 2005-149408	20050609	<--
PRAI	US 2003-491832P	P	20030801	<--		
	US 2004-899641	A	20040727	<--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
WO 2005012249	ICM	C07D213-00	
WO 2005012249	ECLA	C07C255/46; C07C255/47; C07D207/16; C07D209/52; C07D277/04; C07D295/18B1F	<--
US 2005038020	NCL	514/227.500	
	ECLA	C07C255/46; C07C255/47; C07D207/16; C07D209/52; C07D277/04; C07D295/18B1F	<--
US 2005228021	NCL	514/319.000	<--
US 2005239839	NCL	514/319.000	<--

OS MARPAT 142:219555
GI



I

AB Title compds. [I; m, n = 0-2; m+n ≤2; dashed bonds form a cyclopropyl ring when Y = CH; X = H, CN; Y = CH, CH2, CHF, CF2, O, S, SO, SO2; A = (substituted) adamantyl], were prepared Thus, (S)-(3-hydroxy-5,7-dimethyladamantan-1-yl)glycine pyrrolidinamide (preparation from 3,5-dimethyladamantane-1-carboxylic acid given) at 3 μmol/kg orally in rats gave a 39% reduction in serum glucose after 4 h.

ST adamantyglycinamide prepn **dipeptidyl peptidase** IV inhibitor; antidiabetic glycinamide adamantyl prepn

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ALBP (adipocyte lipid-**binding** protein), inhibitors coadministration; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)

IT Lipoprotein receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(LDL, up-regulators coadministration; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(MTP (microsomal triglyceride-exchanging protein), inhibitors coadministration; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)

IT Antiarteriosclerotics
(antiatherosclerotics; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)

IT Hypolipemic agents
(antihypertriglyceridemics; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)

IT Thyroid hormone receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(beta compds., coadministration; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)

IT Proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cholesterol ester-exchanging, coadministration; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)

IT 5-HT reuptake inhibitors
(coadministration; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)

IT Sulfonylureas
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coadministration; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)

IT **Diabetes mellitus**
(complication treatment; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)

IT Kidney, disease
(diabetic nephropathy, treatment; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)

IT Nerve, disease
(diabetic neuropathy, treatment; preparation of adamantyglycinamide

inhibitors of **dipeptidyl peptidase** IV)
IT Eye, disease
(diabetic retinopathy, treatment; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)
IT Fatty acids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(elevated blood levels, treatment; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)
IT Lipids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hyperlipidemia, treatment; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)
IT Drugs
(insulin sensitizers, coadministration; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)
IT Disease, animal
(metabolic syndrome X, treatment; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)
IT **Antidiabetic agents**
Antihypertensives
Antiobesity agents
Combination chemotherapy
Drug delivery systems
Human
Hypolipemic agents
Wound healing
(preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)
IT Amino acids, preparation
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)
IT Atherosclerosis
Diabetes mellitus
Hyperglycemia
Hypertension
Hypertriglyceridemia
Obesity
(treatment; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)
IT Peroxisome proliferator-activated receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α, agonists coadministration; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)
IT Adrenoceptor agonists
(β3-, coadministration; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)
IT Peroxisome proliferator-activated receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ, agonists coadministration; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)
IT 113-00-8, Guanidine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biguanides, coadministration; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)
IT 841302-18-9P 841302-19-0P 841302-20-3P 841302-21-4P 841302-22-5P
841302-23-6P 841302-24-7P 841302-25-8P 841302-26-9P 841302-27-0P
841302-28-1P 841302-29-2P 841302-30-5P 841302-31-6P 841302-32-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(claimed compound; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)
IT 51-64-9, Dexamphetamine 94-20-2, Chloropropamide 122-09-8, Phentermine

637-07-0, Clofibrate **657-24-9, Metformin** 943-45-3D, derivs. 9004-10-8, Insulin, biological studies 10238-21-8, Glyburide 14838-15-4, Phenylpropanolamine 21187-98-4, Gliclazide 22232-71-9, Mazindol 25812-30-0, Gemfibrozil 29094-61-9, Glipizide 49562-28-9, Fenofibrate 54870-28-9, Meglitinide 56180-94-0, Acarbose 72432-03-2, Miglitol 75330-75-5, Lovastatin 79902-63-9, Simvastatin 81093-37-0, Pravastatin 89750-14-1, Glucagon-like peptide 1 93479-97-1, Glimepiride 93957-54-1, Fluvastatin 96829-58-2, Orlistat 97240-79-4, Topiramate 97322-87-7, Troglitazone 105816-04-4, Nateglinide 106650-56-0, Sibutramine 111025-46-8, Pioglitazone 122320-73-4, Rosiglitazone 134523-00-5, Atorvastatin 135062-02-1, Repaglinide 145599-86-6, Cerivastatin 161600-01-7, Isaglitazone 166518-60-1, Avasimibe 287714-41-4, Visastatin 430433-17-3, Glipyride 444069-80-1, Axokine 503538-55-4, Nivastatin
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(coadministration; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)

IT 56-81-5, Glycerol, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(elevated blood levels, treatment; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)

IT 9001-62-1, Lipase 9027-63-8, Acat 9028-35-7, Hmg coa reductase 9029-60-1, Lipoxygenase 9033-06-1, Glucosidase 9077-14-9, Squalene synthetase 335197-46-1, SGLT 2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors coadministration; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)

IT **54249-88-6, Dpp-iv**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)

IT 841302-49-6P 841302-50-9P 841302-51-0P 841302-52-1P 841302-53-2P 841302-57-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)

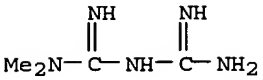
IT 110-89-4, Piperidine, reactions 123-75-1, Pyrrolidine, reactions 503-29-7, Azetidine 504-78-9, Thiazolidine 593-71-5, Chloroiodomethane 828-51-3, Adamantane-1-carboxylic acid 1148-11-4 14670-94-1, 3,5-Dimethyladamantane-1-carboxylic acid 361440-68-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)

IT 711-01-3P 770-71-8P, Tricyclo[3.3.1.13,7]decane-1-methanol 2094-74-8P 58727-83-6P 68471-57-8P 69261-54-7P 69352-21-2P 361441-95-4P 361441-96-5P 361441-97-6P 361442-00-4P 681282-72-4P 841302-34-9P 841302-35-0P 841302-36-1P 841302-37-2P 841302-38-3P 841302-39-4P 841302-40-7P 841302-41-8P 841302-42-9P 841302-43-0P 841302-44-1P 841302-45-2P 841302-46-3P 841302-47-4P 841302-48-5P 841302-54-3P 841302-55-4P 841302-56-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)

IT 51-61-6, Dopamine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(reuptake inhibitors coadministration; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)

IT **657-24-9, Metformin**
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(coadministration; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)

RN 657-24-9 HCAPLUS
CN Imidodicarbonimidic diamide, N,N-dimethyl- (9CI) (CA INDEX NAME)



IT 54249-88-6, Dpp-iv
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; preparation of adamantyglycinamide inhibitors of **dipeptidyl peptidase** IV)
RN 54249-88-6 HCAPLUS
CN Peptidase, dipeptidyl, IV (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L140 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:996119 HCAPLUS
DN 141:406152
ED Entered STN: 19 Nov 2004
TI Glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compositions, and use
IN **Demuth, Hans-Ulrich**; Hoffmann, Matthias; Hoffmann, Torsten; Niestroj, Andre J.; Schilling, Stephan; **Heiser, Ulrich**
PA **Prosidion** Ltd., UK
SO PCT Int. Appl., 497 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D207-00
CC 1-12 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 6

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004099134	A2	20041118	WO 2004-EP4774	20040505 <--
WO 2004099134	A3	20050113		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004229848	A1	20041118	US 2004-839122	20040505 <--
PRAI US 2003-467914P	P	20030505 <--		
US 2003-468014P	P	20030505 <--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004099134	ICM	C07D207-00
WO 2004099134	ECLA	A61K031/00; A61K031/4178; A61K031/4184; A61K031/4188; A61K031/4192; C07D205/04; C07D207/08A; C07D207/10; C07D207/12; C07D207/16; C07D207/20; C07D207/22; C07D207/24; C07D231/04; C07D231/06C; C07D233/02; C07D233/06; C07D233/28; C07D233/42; C07D233/54C; C07D249/04; C07D249/08D; C07D249/10; C07D257/04D2C4; C07D261/04; C07D263/04B; C07D263/06; C07D277/04; C07D277/06; C07D295/18B1F; C07D403/04+257+207; C07D403/04+257+233; C07D403/04+257+241B; C07D413/04+257+263B; C07D413/04+257+265D; C07D417/04+277B+257; C07D417/04+279+257;

C07D471/04+239B+221B; C07D487/04+241C+235C;
C07D487/04+249C+241C; C07F009/572K4; C07F009/59K4;
C07F009/6506K4; C07F009/6561 <--

US 2004229848 NCL 514/114.000
ECLA A61K031/00; A61K031/4178; A61K031/4184; A61K031/4188;
A61K031/4192; C07D233/54C; C07F009/572K4; C07F009/59K4;
C07F009/6506K4; C07F009/6561 <--

AB The invention discloses **dipeptidyl peptidase** IV (DPIV) inhibitors, more particularly, glutaminyl derivs., wherein the glutamine residue is bound in a peptide manner to a moiety which imitates the amino acid residue proline, especially to a nitrogen containing moiety. The invention also discloses pharmaceutical compns. containing these compds., and the use of these compds. in inhibiting DPIV and DPIV-like enzyme activity.

ST glutaminyl deriv proline mimetic compd **dipeptidyl peptidase** IV inhibitor; DPIV inhibitor glutaminyl deriv proline mimetic compd pharmaceutical

IT Inflammation
(Crohn's disease; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Intestine, disease
(Crohn's; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Polynucleotides
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(GLP-1-encoding and GIP-encoding; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GLP-2, agonists; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Heloderma
(Gila monster exendin signal sequence; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Antibodies and Immunoglobulins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Ig κ signal sequence; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Rous sarcoma virus
(LTR sequence; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Promoter (genetic element)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Tet-On/Tet-Off system; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT VIP receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(VIP2, agonists; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Glucagon receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(agonists; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Antiarteriosclerotics
(antiatherosclerotics; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Signal transduction, biological
(at islets of Langerhans; glutaminyl-based **dipeptidyl**

peptidase IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT Prostate gland, disease
(benign hyperplasia; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT Hyperplasia
(benign prostatic; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT Transport proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(bile acid transporter, ileal, inhibitors; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT Human
Primates
Rodentia
(cell; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT Fatigue, biological
Pain
(chronic; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT Nervous system, disease
(degeneration; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT Mental and behavioral disorders
(depression; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT Kidney, disease
(diabetic nephropathy; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT Nerve, disease
(diabetic neuropathy; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT Mucous membrane
(disease; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT Simian virus 40
(early gene promoter; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT Gene, microbial
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(early, SV40 early gene promoter; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT Gastrointestinal hormone receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gastric inhibitory polypeptide, agonists; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT Gingiva, disease
Inflammation
(gingivitis; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(glp-1, agonists; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT Adenoviral vectors
Analgesics

Anti-inflammatory agents
Anticholesteremic agents
Anticonvulsants
Antidepressants
Antidiabetic agents
Antihypertensives
Antiobesity agents
Antioxidants
Antipsychotics
Antitumor agents
Anxiety
Anxiolytics
Atherosclerosis
Autoimmune disease
Cardiovascular agents
Cardiovascular system, disease
Combination chemotherapy
Convulsion
Diabetes mellitus
Drug delivery systems
Epilepsy
Gastrointestinal agents
Gene therapy
Hypercholesterolemia
Hypolipemic agents
Immunomodulators
Inflammation
Lentiviral vectors
Malnutrition
Mental and behavioral disorders
Nervous system agents
Obesity
Osteoporosis
Pancreatic islet of Langerhans
Peroxisome proliferators
Psychotropics
Retroviral vectors
Schizophrenia
Sequestering agents
Skin, disease
Sleep disorders
Viral vectors
(glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Promoter (genetic element)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Sulfonylureas
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Liver
(hepatocyte, human; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Lipids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hyperlipidemia; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Intestine, disease
(inflammatory; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Genetic element

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(long terminal repeat, Rous sarcoma; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Hypertension
(metabolism-related; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Lipids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabolic disorders; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Acidosis
(metabolic; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Neoplasm
(metastasis; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Disease, animal
(mucous membrane; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT **Diabetes mellitus**
(**non-insulin-dependent**; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Enzyme kinetics
(of inhibition; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Inflammation
Pancreas, disease
(pancreatitis; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Genetic element
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(polyadenylation signal; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Disease, animal
(prediabetes; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Cytomegalovirus
(promoter; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Disease, animal
(psychosomatic; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Genetic element
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(signal sequence; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Muscle, disease
(spasm; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Pituitary adenylate cyclase-activating polypeptide receptor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type III, agonists; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Inflammation
Intestine, disease
(ulcerative colitis; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT Biological transport
(uptake, cholesterol absorption inhibitors; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT Adeno-associated virus
(vector; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT Peroxisome proliferator-activated receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α, agonists; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT Peroxisome proliferator-activated receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ, agonists; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT Peroxisome proliferator-activated receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(δ, agonists; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT 213190-65-9, Exendin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Gila monster exendin signal sequence; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT 57-88-5, Cholesterol, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(absorption inhibitors; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT 9004-10-8, Insulin, biological studies
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(and insulin sensitizers, mimetics, and secretagogues; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT 89750-14-1, GLP-1 141732-76-5, Exendin 4 276891-44-2, Glucagon-like peptide-2 receptor (rat)
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(and mimetics; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT 59392-49-3, Glucose-dependent insulinotropic peptide 137061-48-4, PACAP
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(and mimetics; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT **50-99-7**, D-Glucose, biological studies 141760-45-4, Furin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)
IT 51-17-2, Benzimidazole 51-45-6, Histamine, biological studies 71-00-1, L-Histidine, biological studies 274-47-5, Imidazo[1,5-a]pyridine 288-32-4, Imidazole, biological studies 501-75-7 616-47-7, 1-Methylimidazole 644-42-8 668-94-0, 4,5-Diphenylimidazole 673-49-4 931-36-2, 2-Ethyl-4-methylimidazole 934-32-7, 2-Aminobenzimidazole 1072-63-5, 1-Vinylimidazole 1122-28-7, 4,5-Dicyanoimidazole 2466-76-4, N-Acetylimidazole 3034-50-2, 4-Imidazole carboxaldehyde 4238-71-5, 1-Benzylimidazole 4836-52-6, L-Histidinol 4857-06-1, 2-Chloro-1H-benzimidazole 5036-48-6, 1-(3-Aminopropyl)imidazole 7164-98-9, 1-Phenylimidazole 7189-69-7, 1,1'-Sulfonyldiimidazole 7621-14-9, L-Histidinamide 10364-94-0, N-Benzoylimidazole 13750-62-4, 2-Methyl-n-benzylimidazole 18156-74-6, N-(Trimethylsilyl)imidazole 23403-90-9 24155-34-8 29636-87-1, 5-Hydroxymethyl-4-methylimidazole

78218-09-4 219139-36-3 219619-43-9 287198-17-8 658073-89-3
791596-11-7 791596-17-3 791596-19-5 791596-25-3 791596-27-5
791596-30-0
RL: PAC (Pharmacological activity); BIOL (Biological study)
(glutaminyl-based **dipeptidyl peptidase** IV (DPIV)
inhibitors, pharmaceutical compns., and use)

IT 56-03-1D, Biguanide, derivs. 56-85-9D, Glutamine, derivs. 59-67-6, Nicotinic acid, biological studies 100-55-0, Nicotinyl alcohol **657-24-9, Metformin** 56180-94-0, Acarbose 141758-74-9, AC-2993 197922-42-2, ALX-0600 204656-20-2, NN-2211
RL: PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(glutaminyl-based **dipeptidyl peptidase** IV (DPIV)
inhibitors, pharmaceutical compns., and use)

IT 9001-42-7, α-Glucosidase 9027-63-8, Acyl-CoA:cholesterol acyltransferase 9028-35-7, HMG-CoA reductase 53414-63-4, Glutaminyl cyclase **54249-88-6, Dipeptidyl peptidase** IV
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

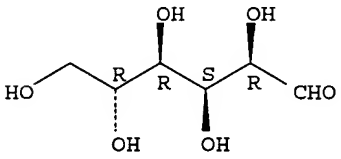
IT 300865-11-6, Protein tyrosine phosphatase 1B
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT 147-85-3, Proline, biological studies 251571-74-1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mimetics; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

IT **50-99-7**, D-Glucose, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(glutaminyl-based **dipeptidyl peptidase** IV (DPIV)
inhibitors, pharmaceutical compns., and use)

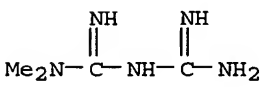
RN 50-99-7 HCAPLUS
CN D-Glucose (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **657-24-9, Metformin**
RL: PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(glutaminyl-based **dipeptidyl peptidase** IV (DPIV)
inhibitors, pharmaceutical compns., and use)

RN 657-24-9 HCAPLUS
CN Imidodicarbonimidic diamide, N,N-dimethyl- (9CI) (CA INDEX NAME)



IT **54249-88-6, Dipeptidyl peptidase** IV
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; glutaminyl-based **dipeptidyl peptidase** IV (DPIV) inhibitors, pharmaceutical compns., and use)

RN 54249-88-6 HCAPLUS
CN Peptidase, dipeptidyl, IV (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L140 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:308518 HCAPLUS
DN 140:334648
ED Entered STN: 15 Apr 2004
TI **Secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compounds, and therapeutic uses thereof
IN Kuehn-Wache, Kerstin; **Baer, Joachim**; **Demuth, Hans-Ulrich** ; Hoffmann, Torsten; **Heiser, Ulrich**; **Brandt, Wolfgang**
PA **Probiodrug** A.-G., Germany
SO PCT Int. Appl., 152 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N009-00
CC 7-3 (Enzymes)
Section cross-reference(s): 1, 6, 13
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 2004031374	A2	20040415	WO 2003-EP10408	20030918	<--
	WO 2004031374	A3	20040812			
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
	US 2004058876	A1	20040325	US 2002-246817	20020918	<--
	EP 1543023	A2	20050622	EP 2003-788909	20030918	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
	US 2005176622	A1	20050811	US 2003-667200	20030918	<--
PRAI	US 2002-246817	A	20020918	<--		
	US 2003-443417P	P	20030129	<--		
	WO 2003-EP10408	W	20030918	<--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
WO 2004031374	ICM	C12N009-00	
WO 2004031374	ECLA	A61K031/401; C07K007/06B	<--
US 2004058876	NCL	514/017.000	
	ECLA	A61K031/401; C07K007/06A	<--
EP 1543023	ECLA	A61K031/401; C07K007/06B	<--
US 2005176622	NCL	514/002.000	<--

AB The present application relates to the **secondary binding** site of **dipeptidyl peptidase** IV, its relationship amongst substrates and to the modulation of substrate specificity of **dipeptidyl peptidase** IV (DP IV, synonym: **DPP IV**, CD26, **EC 3.4.14.** 5). The application relates further to compds. that **bind** to the **secondary binding** site of DP IV and their use to modulate the substrate specificity of DP IV; methods of treatment of various DP IV mediated disorders; and screening methods for the identification of **secondary binding** sites on DP IV and DP IV-like enzymes. The **binding** and hydrolysis of small dipeptide substrates was only slightly influenced when DP IV was preincubated with the hexapeptides TFTSDY and TFTDDY or the degradation stabilized heptapeptide H-Ser-D-Glu-Thr-Gly-D-Val-D-Lys-D-Val-OH, but the

affinity of larger oligopeptides such as GIP, VIP, and glucagon was reduced. These expts. and others identify a **secondary binding** site.

ST mammal **dipeptidyl peptidase** IV substrate **binding** site modulating drug

IT Inflammation
(Crohn's disease; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Intestine, disease
(Crohn's; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT RANTES (chemokine)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(RANTES1-15, substrate; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT VIP receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(VIP2, agonist; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Enzyme functional sites
(active; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Neuropeptide Y receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(agonist and antagonist; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Glucagon receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(agonist; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Protein sequences
(alignment, consensus substrate; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Prostate gland, disease
(benign hyperplasia; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Hyperplasia
(benign prostatic; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Transport proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(bile acid transporter, inhibitor; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Fatigue, biological

(chronic fatigue syndrome; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Pain
(chronic; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Nervous system, disease
(degeneration; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Mental and behavioral disorders
(depression; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Nerve, disease
(diabetic neuropathy; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Mucous membrane
(disease; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Lipids, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(disorders; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Lipids, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(dyslipidemia; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Gastrointestinal hormone receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gastric inhibitory polypeptide, agonist; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Gingiva, disease
Inflammation
(gingivitis; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT G protein-coupled receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(glucagon-like peptide-1 (GLP-1), agonist; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT G protein-coupled receptors
Hormone receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(glucagon-like peptide-2, agonist; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Lipoproteins
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(high-d., low level; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)
IT Lipids, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(hyperlipidemia; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)
IT Intestine, disease
(inflammatory; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)
IT Self-association
(inhibition; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)
IT Bond
(ionic, salt bridge; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)
IT Intestine, disease
(irritable bowel syndrome; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)
IT Lipoproteins
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(low-d., high level; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)
IT Disease, animal
(metabolic syndrome X; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)
IT Acidosis
(metabolic; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)
IT Neoplasm
(metastasis; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)
IT Simulation and Modeling, physicochemical
(mol. dynamics; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)
IT Disease, animal
(mucous membrane; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)
IT Agranulocytosis
(neutropenia; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its

substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Crystal structure
(of porcine **dipeptidyl peptidase** IV)

IT Inflammation
Pancreas, disease
(pancreatitis; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Ovary, disease
(polycystic; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Quaternary structure
(protein; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Artery, disease
(restenosis; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Eye, disease
(retinopathy; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Peptides, biological studies
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**secondary binding** site effector; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Anti-inflammatory agents
Anticholesteremic agents
Antidiabetic agents
Antihypertensives
Antiobesity agents
Antioxidants
Anxiety
Atherosclerosis
Autoimmune disease
Cardiovascular system, disease
Conformation
Convulsion
Diabetes mellitus
Drug screening
Drug targets
Epilepsy
Human
Hydrogen bond
Hypercholesterolemia
Hyperglycemia
Hypertension
Hypertriglyceridemia
Immunomodulators
Inflammation
Kidney, disease
Malnutrition
Mammalia
Mental and behavioral disorders
Michaelis constant

Molecular modeling
Molecular recognition
Nervous system agents
Obesity
Osteoporosis
Peroxisome proliferators
Protein degradation
Schizophrenia
Skin, disease
Sleep disorders
Sus scrofa domestica
(**secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Sulfonylureas
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Muscle, disease
(spasm; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Enzyme functional sites
(substrate-**binding**; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Thromboxane receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(substrate; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(tat, substrate; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Pituitary adenylate cyclase-activating polypeptide receptor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type III, agonist; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Inflammation
Intestine, disease
(ulcerative colitis; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Peroxisome proliferator-activated receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α, agonist; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Peroxisome proliferator-activated receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ, agonist; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT Peroxisome proliferator-activated receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(δ, agonist; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT 9002-72-6, Growth hormone
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(deficiency; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT 9027-63-8, Acyl CoA:cholesterol acyltransferase 9028-35-7, HMG-CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT 680227-81-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(inhibitor; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT 9001-42-7, α-Glucosidase 300865-11-6, Protein tyrosine phosphatase-1B
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT **50-99-7**, D-Glucose, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(intolerance and glucosuria; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT 72-19-5, L-Threonine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(residue 152; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT 71-00-1, L-Histidine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(residue 363; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT 73-32-5, L-Isoleucine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(residue 407; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT 56-45-1, L-Serine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(residue 460; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT 56-87-1, L-Lysine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(residue 463; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic

uses thereof)
IT 61-90-5, L-Leucine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(residue 90; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)
IT 73-22-3, L-Tryptophan, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(residues 154 and 157; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)
IT 74-79-3, L-Arginine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(residues 310, 318, and 560; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)
IT 60-18-4, L-Tyrosine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(residues 330 and 416; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)
IT 56-86-0, L-Glutamic acid, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(residues 91, 361 and 464; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)
IT 680227-76-3 680227-77-4 680227-78-5 680227-79-6
RL: BUU (Biological use, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**secondary binding** site effector; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)
IT **54249-88-6P, E.C. 3.4.14.5**
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(**secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)
IT **497682-34-5**, GenBank AY198323
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(**secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)
IT 56-03-1, Biguanide 59-67-6, Nicotinic acid, biological studies
100-55-0, Nicotinyl alcohol **114-86-3, Phenformin 657-24-9, Metformin 692-13-7, Buformin** **9004-10-8**, Insulin, biological studies 56180-94-0, Acarbose
59392-49-3, Gastric inhibitory polypeptide 82785-45-3, Neuropeptide Y
89750-14-1, Glucagon-like peptide I 89750-15-2, Glucagon-like peptide 2
137061-48-4, Pituitary adenylate cyclase-activating polypeptide
141732-76-5, Exendin 4 141758-74-9, Exenatide
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(**secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)
IT 9007-92-5, Glucagon, biological studies 128606-20-2, PACAP 38
129069-75-6, PACAP 27
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(substrate; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT 121-44-8, Triethylamine, reactions 288-32-4, Imidazole, reactions 115630-49-4 680227-83-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of DP IV inhibitor; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

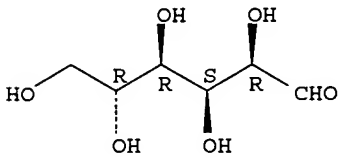
IT 680227-80-9P 680227-82-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of DP IV inhibitor; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT 674787-38-3 674787-40-7 674787-48-5 674787-53-2 680594-87-0 680656-62-6 680656-63-7 680656-64-8 680656-65-9 680656-66-0 680656-67-1 680656-68-2 680656-69-3
RL: PRP (Properties)
(unclaimed sequence; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

IT **50-99-7**, D-Glucose, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(intolerance and glucosuria; **secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

RN 50-99-7 HCAPLUS
CN D-Glucose (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **54249-88-6P, E.C. 3.4.14.5**
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(**secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

RN 54249-88-6 HCAPLUS
CN Peptidase, dipeptidyl, IV (9CI) (CA INDEX NAME)

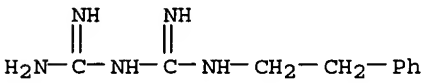
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **497682-34-5**, GenBank AY198323
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(**secondary binding** site of **dipeptidyl peptidase** IV (DP IV), modulation of its substrate specificity, **binding**-site compds., and therapeutic uses thereof)

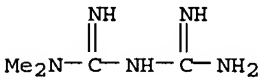
RN 497682-34-5 HCAPLUS
CN DNA (swine gene DPPIV cDNA plus flanks) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

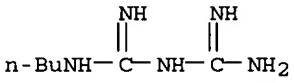
IT **114-86-3, Phenformin 657-24-9, Metformin 692-13-7, Buformin 9004-10-8**
, Insulin, biological studies
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(secondary binding site of dipeptidyl peptidase IV (DP IV), modulation of its substrate specificity, binding-site compds., and therapeutic uses thereof)
RN 114-86-3 HCAPLUS
CN Imidodicarbonimidic diamide, N-(2-phenylethyl)- (9CI) (CA INDEX NAME)



RN 657-24-9 HCAPLUS
CN Imidodicarbonimidic diamide, N,N-dimethyl- (9CI) (CA INDEX NAME)



RN 692-13-7 HCAPLUS
CN Imidodicarbonimidic diamide, N-butyl- (9CI) (CA INDEX NAME)



RN 9004-10-8 HCAPLUS
CN Insulin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L140 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2004:41516** HCAPLUS
DN 140:105831
ED Entered STN: 18 Jan 2004
TI Pharmaceutical compositions and uses of GLP-1 mimetics for the treatment of diabetes
IN Steiness, Eva
PA Zealand Pharma A/S, Den.
SO PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07K014-575
ICS C07K014-605; A61K038-26; A61P003-10; C12N005-06; A61K047-48
CC 2-6 (Mammalian Hormones)
Section cross-reference(s): 63
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004005342	A1	20040115	WO 2003-DK463	20030702 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,

KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
CA 2490564 AA 20040115 CA 2003-2490564 20030702 <--
EP 1525219 A1 20050427 EP 2003-762471 20030702 <--
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IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
PRAI US 2002-393917P P 20020704 <--
US 2003-465613P P 20030424 <--
WO 2003-DK463 W 20030702 <--

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004005342	ICM	C07K014-575
	ICS	C07K014-605; A61K038-26; A61P003-10; C12N005-06; A61K047-48
WO 2004005342	ECLA	A61K038/22; A61K038/26; A61K038/28+M; A61K038/31+M <--

AB The present invention relates to use of GLP-1 or a related mol. having GLP-effect for the manufacture of a medicament for preventing or treating diabetes in a mammal. The amount and timing of administration of said medicament are subsequently reduced to produce a 'drug holiday'. Practice of the invention achieves effective therapy without continuous drug exposure and without continuous presence of therapeutic levels of the drug. The invention also discloses a method of treating diabetes and related disorders in a mammal by administering glucagon like peptide (GLP-1) or a related mol. having GLP-1 like effect and thereby providing a therapeutically effective amount of endogenous insulin.

ST GLP1 mimetics treatment diabetes insulin glucose tolerance intermittent pharmacotherapy

IT Endocrine system, disease
Pancreas, disease
Prader-Willi syndrome
(-related diabetes; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)

IT **Diabetes mellitus**
(**MODY (maturity-onset diabetes of the young)**; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)

IT Glucagon-like peptide-1 receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(activation by GLP-1 of GLP-1 mimetic; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)

IT Disease, animal
(adipose tissue, -related diabetes; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)

IT Drug delivery systems
(bolus; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)

IT **Antidiabetic agents**
(co-administration with GLP-1 mimetic; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)

IT Sulfonylureas
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(co-administration with GLP-1 mimetic; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)

IT Adipose tissue
(disease, -related diabetes; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)

IT Disease, animal
(genetic, -related diabetes; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)

IT Hemoglobins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(glycohemoglobins, test, as a marker point for treatment continuity; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of

diabetes)
IT Autoimmune disease
(insulin-dependent diabetes mellitus; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)
IT **Diabetes mellitus**
(**insulin-dependent**; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)
IT Chemotherapy
(intermittent treatment; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)
IT Endocrine system, disease
(leprechaunism; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)
IT Disease, animal
(metabolic syndrome X, -related diabetes; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)
IT Insulin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mutation, causing leprechaunism; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)
IT **Diabetes mellitus**
(**non-insulin-dependent**; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)
IT Inflammation
Pancreas, disease
(pancreatitis; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)
IT **Diabetes mellitus**
Human
(pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)
IT **Diabetes mellitus**
(tropical or **secondary** to other diseases and syndromes; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)
IT Pancreatic islet of Langerhans
(β-cell, function; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)
IT 9004-10-8, Insulin, biological studies
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(co-administration with GLP-1 mimetic; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)
IT 56-03-1, Biguanide 64-77-7, Tolbutamide 94-20-2, Chloropropamide **114-86-3, Phenformin** 364-98-7, Diazoxide **657-24-9, Metformin** 968-81-0, Acetohexamide 1156-19-0, Tolazamide 2295-31-0, Thiazolidinedione 9004-10-8D, Insulin, analogs and derivs. 10238-21-8, Glyburide 11070-73-8, Bovine insulin 12584-58-6, Porcine insulin 21187-98-4, Gliclazide 29094-61-9, Glipizide 51110-01-1, Somatostatin 56180-94-0, Acarbose 74772-77-3, Ciglitazone 111025-46-8, Pioglitazone 133107-64-9, Lys (B28), Pro (B29) human insulin
RL: PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(co-administration with GLP-1 mimetic; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)
IT **50-99-7**, Glucose, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(fasting **blood**, as a marker point for treatment continuity; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)
IT 56-12-2, γ-Aminobutyric acid, biological studies 107-95-9, β-Alanine 13406-98-9, 1-Piperidinecarboxylic acid 14464-30-3 14565-47-0 22102-66-5 25456-76-2 55889-33-3 111333-92-7 176435-11-3 240133-29-3 240133-30-6 240133-31-7 240133-32-8 240133-33-9 240133-34-0 240133-35-1 240133-36-2 240133-37-3

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240133-43-1 240133-44-2 240133-45-3 240133-46-4 240133-47-5
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240480-98-2 240480-99-3 240481-01-0 240481-02-1 240481-03-2
240481-04-3 240481-05-4 240481-06-5 240481-07-6 240481-08-7
240481-09-8 240481-10-1 240481-11-2 240481-12-3 240481-13-4
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240481-33-8 240481-35-0 240481-37-2 240481-39-4 240482-41-1
240482-42-2 240482-43-3 240482-44-4 240482-45-5 240483-55-0
240483-71-0 240497-59-0
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glucagon-like peptide conjugates; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)

IT 9001-42-7, α-Glucosidase
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitor, co-administration with GLP-1 mimetic; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)

IT 9007-92-5, Glucagon, biological studies 33507-63-0, Substance P 33515-09-2, Luteinizing hormone-releasing factor (swine) 52232-67-4 58822-25-6, Leucine enkephalin 59392-49-3, Gastric inhibitory polypeptide 62568-57-4, Delta sleep-inducing peptide (rabbit) 87805-34-3, Glucagon-like peptide I (human) 87805-34-3D, Glucagon-like peptide I (human), lipophilic derivs. 89750-14-1, Glucagon-like peptide I 89750-14-1D, Glucagon-like peptide I, GLP-I (7-36) and GLP-I (7-37) variants, conjugates containing 89750-14-1D, Glucagon-related peptide I, lipophilic derivs. 89750-14-1D, Glucagon-like peptide I, mimetics 89750-15-2, Glucagon-like peptide II 93438-37-0, Helospectin I 93585-83-2, Helospectin II 99658-04-5D, lipophilic derivs. 104211-94-1 104364-62-7D, Glucagon-related peptide I (guinea pig clone gpGCG-2), lipophilic derivs. 106612-94-6, 7-37-Glucagon-like peptide I (human) 106612-94-6D, Glucagon-like peptide I(7-37) (human), lipophilic derivs. 107444-51-9 107444-51-9D, lipophilic derivs. 119637-73-9 121181-17-7, Glucagon-like peptide 1 (Octodon degus) 121181-17-7D, Glucagon-related peptide 1 (Octodon degus), lipophilic derivs. 123475-27-4D, lipophilic derivs. 123475-28-5D, 7-35-Glucagon-like peptide I (human), lipophilic derivs. 123512-62-9D, lipophilic derivs. 127650-06-0, 7-34-Glucagon-like peptide I (human) 130357-25-4, Exendin 3 (Heloderma horridum) 130391-54-7, Exendin-3 130391-54-7D, Exendin-3, analogs and derivs. 133514-43-9, 9-39-Exendin 3 (Heloderma horridum) 135062-02-1 138324-89-7 138324-90-0 138324-91-1 138324-92-2 138324-93-3 138324-94-4 138324-95-5 138324-96-6 138324-97-7 138324-98-8 138324-99-9 138325-00-5 138325-01-6 138347-75-8 138347-76-9 138347-77-0 141732-76-5, Exendin-4 141732-76-5D, Exendin-4, analogs and derivs. 141758-74-9, Exendin-4 (Heloderma suspectum) 144623-81-4 151743-77-0 151743-78-1 151743-79-2 157569-66-9D, lipophilic derivs. 157629-57-7D, lipophilic derivs. 158345-16-5 165338-05-6, 1-31-Exendin 4 (Heloderma suspectum) 165338-06-7 170098-75-6D, peptide conjugates 170851-70-4 180201-29-0 194551-05-8 203743-26-4 203743-27-5 203743-28-6 203743-29-7 203743-30-0 203743-31-1 203743-32-2 203743-33-3 203743-35-5 203743-36-6 203743-37-7 203743-38-8 203743-39-9 203743-40-2 203743-41-3 203743-42-4 203743-43-5 203743-44-6 203743-45-7 203743-46-8 203743-47-9 203743-48-0 203743-49-1 203743-50-4 203743-51-5 203743-52-6 203743-53-7 203743-54-8 203743-55-9 204521-54-0 204521-55-1 204521-56-2 204521-57-3 204521-58-4 204521-59-5 204521-68-6D, lipophilic derivs. 204521-69-7D, lipophilic derivs. 204521-70-0D, lipophilic derivs. 204521-72-2D, lipophilic derivs. 204521-81-3D, lipophilic derivs. 204521-82-4D, lipophilic derivs. 204521-83-5D, lipophilic derivs. 204521-84-6D, lipophilic derivs. 204521-85-7D, lipophilic derivs. 204521-86-8D, lipophilic derivs. 204521-87-9D, lipophilic derivs. 204521-88-0D, lipophilic derivs. 204521-89-1D, lipophilic derivs. 204521-90-4D, lipophilic derivs. 204521-91-5D, lipophilic derivs. 204521-92-6D, lipophilic derivs. 204655-84-5D, lipophilic derivs. 204655-85-6D, lipophilic

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RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
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(pharmaceutical compns. and uses of GLP-1 mimetics for treatment of
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RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
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(pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)

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RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)

IT 320370-26-1 320370-32-9 320370-65-8 320370-68-1 320370-71-6
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RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(unclaimed protein sequence; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)

RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
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IT **114-86-3, Phenformin 657-24-9, Metformin**
RL: PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(co-administration with GLP-1 mimetic; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)

RN 114-86-3 HCAPLUS
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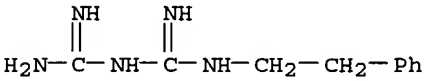

RN 657-24-9 HCAPLUS
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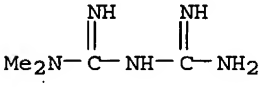
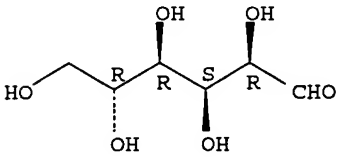


IT **50-99-7**, Glucose, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(fasting **blood**, as a marker point for treatment continuity; pharmaceutical compns. and uses of GLP-1 mimetics for treatment of diabetes)

RN 50-99-7 HCAPLUS
CN D-Glucose (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



L140 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:51257 HCAPLUS
DN 136:123595
ED Entered STN: 18 Jan 2002
TI A combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for the treatment of diabetes
IN Van Poelje, Paul D.; Erion, Mark D.; Fujiwara, Toshihiko
PA Metabasis Therapeutics, Inc., USA; Sankyo Company, Ltd.
SO PCT Int. Appl., 392 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-00
CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 1, 27, 28, 29

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002003978	A2	20020117	WO 2001-US21557	20010705
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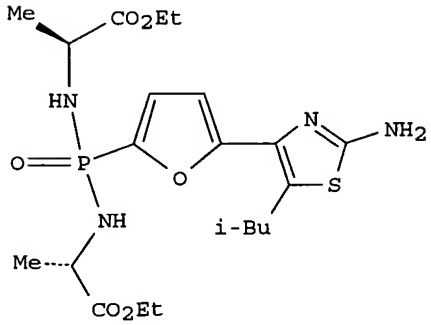
	US 2001-900364	A	20010705		
	US 2000-215126P	P	20000629		
	WO 2001-US21557	W	20010705		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002003978	ICM	A61K031-00
WO 2002003978	ECLA	A61K031/426; A61K045/06
US 2003073728	NCL	514/369.000
	ECLA	A61K031/175; A61K031/426; A61K045/06
JP 2004508297	FTERM	4C084/AA20; 4C084/MA02; 4C084/MA52; 4C084/NA05; 4C084/NA14; 4C084/ZA701; 4C084/ZC022; 4C084/ZC032; 4C084/ZC202; 4C084/ZC351; 4C084/ZC751; 4C086/AA01; 4C086/AA02; 4C086/DA21; 4C086/DA38; 4C086/MA02; 4C086/MA04; 4C086/MA52; 4C086/NA05; 4C086/NA14; 4C086/ZA70; 4C086/ZC02; 4C086/ZC03; 4C086/ZC20; 4C086/ZC35; 4C086/ZC75

OS MARPAT 136:123595

GI



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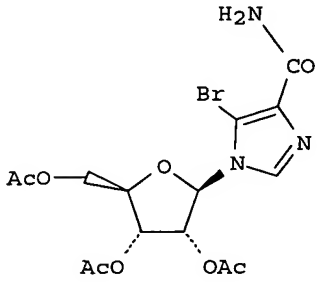

II

AB A combination therapy of at least one FBPase inhibitor ((R1Y)2P(O)M and R14C(O)(CR12R13)nN(R18)P(O)(NR15R16)M; e.g. 2-amino-5-propylthio-4-(5-phosphono-2-furanyl)thiazole monohydrobromide and 2-amino-5-isobutyl-4-[2-

[N,N'-bis[(S)-1-(ethoxycarbonyl)ethyl]phosphonodiamido]-5-furanyl]thiazole (shown as I)) and at least one other antidiabetic agent (insulin secretagogue; e.g. glyburide, a sulfonylurea) is disclosed. (R1Y)2P(O)M and R14C(O)(CR12R13)nN(R18)P(O)(NR15R16)M are converted in vivo or in vitro to MPO32-, which inhibit FBPase; the substituents are defined in the claims. General methods and about 15 specific example prepns. of the phosphorus compds. are included but no methods of preparation are claimed. In the biol. examples, data is presented for the following for selected phosphorus compds. and other materials: inhibition of human liver FBPase, inhibition of rat liver and mouse liver FBPase, inhibition of gluconeogenesis by an FBPase inhibitor in rat hepatocytes, inhibition of glucose production and elevation of fructose-1,6-bisphosphate levels in rat hepatocytes treated with FBPase inhibitors, anal. of hepatic and plasma drug metabolite levels, blood glucose, and hepatic fructose 1,6-bisphosphate levels after administration of compound A (shown as II) p.o. to normal fasted rats, anal. of hepatic and plasma drug levels after administration of compds. i.p. to normal fasted rats, oral bioavailability determination of two compds. and oral glucose lowering activity of two compds. For insulin secretagogues: insulin release from pancreatic islets, glucose lowering in the fasted rat, i.v. glucose tolerance in the fasted rat, oral glucose tolerance in the Zucker diabetic fatty rat, insulin secretion in the rat, inhibition of KATP-channels in mouse pancreatic beta-cells, and sulfonylurea receptor **binding.** Also included are: inhibition of **dipeptidyl peptidase** IV (**DPP-IV** inhibitors), alpha-glucosidase assay, glycogen phosphorylase assay, assay of glucose 6-phosphatase inhibitors, glucagon antagonist assay, amylin agonist assay, fatty acid oxidation inhibitor assay, glucose lowering in the db/db mouse (FBPase inhibitor), glucose lowering in the ZDF rat, acute combination treatment of an insulin secretagogue and an FBPase inhibitor in the ZDF rat, chronic combination treatment of an insulin secretagogue and an FBPase inhibitor in the ZDF rat, acute combination treatment of insulin and an FBPase inhibitor in db/db mice, beneficial effect of chronic combination treatment of insulin and an FBPase inhibitor in db/db mice, and beneficial effect of chronic combination treatment of insulin and an FBPase inhibitor in db/db Mice. Also included are: acute combination treatment of insulin and an FBPase inhibitor in the Goto-Kakizaki rat, acute combination treatment of a biguanide and an FBPase inhibitor in db/db mice, acute combination treatment of an alpha glucosidase inhibitor and an FBPase inhibitor in Goto-Kakizaki rats, acute combination treatment of a glycogen phosphorylase inhibitor and an FBPase inhibitor in db/db or ob/ob mice, acute combination treatment of a glucose-6-phosphatase inhibitor and an FBPase inhibitor in db/db or ob/ob mice, acute combination treatment of an FBPase inhibitor and an amylin agonist, chronic combination treatment of a fatty acid oxidation inhibitor and an FBPase inhibitor in the streptozotocin-induced diabetic rat.

ST antidiabetic agent phosphonate phosphorodiamidate FBPase inhibitor diabetes treatment; insulin secretagogue phosphonate phosphorodiamidate FBPase inhibitor diabetes treatment

IT Potassium channel
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ATP-sensitive; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT Glucagon-like peptide-1 receptors
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(agonists; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT Sulfonylurea receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(binding; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT Antiobesity agents
(combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful as)

IT **Antidiabetic agents**
B cell (lymphocyte)

Drug bioavailability
Human
Pancreatic islet of Langerhans
(combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT Antioxidants
(fatty acid; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT Liver
(fructose bisphosphatase of; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT Liver
(hepatocyte, fructose bisphosphatase of; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT Gluconeogenesis
(inhibitors; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT Fatty acids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT Sulfonylureas
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(insulin secretagogues; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT Drug delivery systems
(oral; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT Organic compounds, biological studies
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(phosphorus-containing; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT Drug delivery systems
(prodrugs; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT 106602-62-4, Amylin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(agonists; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT 151126-32-8, Pramlintide
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amylin agonist; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT 9007-92-5, Glucagon, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antagonists; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT 50-99-7, D-Glucose, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(blood; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT 213125-12-3P, 5-Diethylphosphono-2-(4-methyl-1-oxopentyl)furan
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT 261365-06-4P, 5-Diethylphosphono-2-acetylfuran 261365-08-6P, 5-Diethylphosphono-2-(1-oxobutyl)furan 261365-11-1P, 2-Amino-5-isobutyl-4-[5-phosphono-2-furanyl]thiazole 261365-17-7P 261365-19-9P, 2-Methyl-4-(5-phosphono-2-furanyl)thiazole 261365-23-5P, 2-Isopropyl-4-(5-phosphono-2-furanyl)thiazole 261365-25-7P, 5-Isobutyl-4-(5-phosphono-2-furanyl)thiazole 261365-27-9P, 2-Aminothiocarbonyl-4-(5-phosphono-2-furanyl)thiazole 261365-31-5P 261365-33-7P, 2-(2-Thienyl)-5-isobutyl-4-(5-phosphono-2-furanyl)thiazole 261365-36-0P 261365-37-1P, 2-Acetamido-5-isobutyl-4-(5-phosphono-2-furanyl)thiazole 261365-38-2P, 2-Amino-4-(5-phosphono-2-furanyl)thiazole 261365-40-6P, 2-Methylamino-5-isobutyl-4-(5-phosphono-2-furanyl)thiazole 261365-44-0P 261365-48-4P 261365-51-9P 261365-55-3P 261365-56-4P, 2-Ethoxycarbonyl-4-(5-phosphono-2-furanyl)thiazole 261365-58-6P, 2-Amino-5-ethyl-4-(5-phosphono-2-furanyl)thiazole 261365-60-0P, 2-Cyanomethyl-4-(5-phosphono-2-furanyl)thiazole 261365-62-2P 261365-63-3P, 2-Amino-5-propyl-4-(5-phosphono-2-furanyl)thiazole 261365-65-5P 261365-66-6P, 2-Amino-5-methylthio-4-(5-phosphono-2-furanyl)thiazole 261365-67-7P, 2-Amino-5-cyclopropyl-4-(5-phosphono-2-furanyl)thiazole monohydrobromide 261365-68-8P, 2-Amino-5-cyclopropyl-4-(5-phosphono-2-furanyl)thiazole 261365-70-2P, 2-Amino-5-benzyloxycarbonyl-4-(5-phosphono-2-furanyl)thiazole 261365-72-4P 261365-73-5P, 2-Amino-5-[N,N-dimethylaminomethyl]-4-(5-phosphono-2-furanyl)thiazole dihydrobromide 261365-75-7P, 2-Amino-5-methoxycarbonyl-4-(5-phosphono-2-furanyl)thiazole 261365-78-0P, 2-Amino-5-propyloxycarbonyl-4-(5-phosphono-2-furanyl)thiazole 261365-79-1P, 2-Amino-5-benzyl-4-(5-phosphono-2-furanyl)thiazole 261365-80-4P, 2-Amino-5-[N,N-diethylaminomethyl]-4-(5-phosphono-2-furanyl)thiazole dihydrobromide 261365-83-7P, 2-Amino-5-(N,N-dimethylcarbamoyl)-4-(5-phosphono-2-furanyl)thiazole 261365-85-9P, 2-Amino-5-carboxy-4-(5-phosphono-2-furanyl)thiazole 261365-86-0P, 2-Amino-5-isopropyloxycarbonyl-4-(5-phosphono-2-furanyl)thiazole 261365-89-3P, 2-Methyl-5-cyclopropyl-4-(5-phosphono-2-furanyl)thiazole 261365-90-6P, 2-Methyl-5-ethoxycarbonyl-4-(5-phosphono-2-furanyl)thiazole 261365-92-8P, 2-[N-Acetylamino]-5-methoxymethyl-4-(5-phosphono-2-furanyl)thiazole 261365-95-1P, 2-Amino-5-cyclopropylmethoxycarbonyl-4-(5-phosphono-2-furanyl)thiazole 261365-98-4P, 2-[(N-Dansyl)amino]-5-isobutyl-4-(5-phosphono-2-furanyl)thiazole 261365-99-5P, 2-Amino-5-(2,2,2-trifluoroethyl)-4-(5-phosphono-2-furanyl)thiazole 261366-00-1P, 2-Methyl-5-methylthio-4-(5-phosphono-2-furanyl)thiazole 261366-01-2P, 2-Amino-5-methylthio-4-(5-phosphono-2-furanyl)thiazole monoammonium salt 261366-02-3P, 2-Cyano-5-ethyl-4-(5-phosphono-2-furanyl)thiazole 261366-03-4P, 2-Amino-5-hydroxymethyl-4-(5-phosphono-2-furanyl)thiazole 261366-05-6P, 2-Cyano-5-isobutyl-4-(5-phosphono-2-furanyl)thiazole 261366-06-7P, 2-Amino-5-isopropylthio-4-(5-phosphono-2-furanyl)thiazole monohydrobromide 261366-07-8P, 2-Amino-5-phenylthio-4-(5-phosphono-2-furanyl)thiazole 261366-08-9P, 2-Amino-5-tert-butylthio-4-(5-phosphono-2-furanyl)thiazole 261366-09-0P, 2-Amino-5-propylthio-4-(5-phosphono-2-furanyl)thiazole monohydrobromide 261366-11-4P, 2-Amino-5-ethylthio-4-(5-phosphono-2-furanyl)thiazole 261366-12-5P, 2-[N-(tert-Butyloxycarbonyl)amino]-5-methoxymethyl-4-(5-phosphono-2-furanyl)thiazole 261366-13-6P, 2-Hydroxy-4-(5-phosphono-2-furanyl)thiazole 261366-14-7P, 2-Hydroxy-5-ethyl-4-(5-phosphono-2-furanyl)thiazole 261366-16-9P, 2-Hydroxy-5-isopropyl-4-(5-phosphono-2-furanyl)thiazole 261366-17-0P, 2-Hydroxy-5-isobutyl-4-(5-phosphono-2-furanyl)thiazole 261366-18-1P, 5-Ethoxycarbonyl-4-(5-phosphono-2-furanyl)thiazole 261366-20-5P, 2-Amino-5-vinyl-4-(5-phosphono-2-furanyl)thiazole 261366-21-6P, 2-Methylthio-5-isobutyl-4-(5-phosphono-2-furanyl)thiazole 261366-24-9P, 2-Amino-5-isobutyl-4-(5-phosphono-2-furanyl)selenazole 261366-26-1P, 2-Amino-5-methylthio-4-(5-phosphono-2-furanyl)selenazole 261366-40-9P, 2-Amino-5-(2-furanyl)-4-(5-phosphono-2-furanyl)thiazole 261366-65-8P, 2-Amino-5-isobutyl-4-(5-phosphono-2-furanyl)oxazole 261366-66-9P, 2-Hydroxy-5-isobutyl-4-(5-phosphono-2-furanyl)imidazole 261366-67-0P, 2-Methyl-4-isobutyl-5-(5-phosphono-2-furanyl)oxazole monohydrobromide 261366-68-1P, 2-Methyl-5-isobutyl-4-(5-phosphono-2-furanyl)oxazole monohydrobromide 261366-69-2P, 2-Methyl-5-isobutyl-4-(5-phosphono-2-

furanyl)imidazole monohydrobromide 261366-71-6P, 2-Trifluoromethyl-4-(5-phosphono-2-furanyl)imidazole 261366-73-8P, 4,5-Dimethyl-1-isobutyl-2-(5-phosphono-2-furanyl)imidazole 261366-74-9P, 2-Amino-5-propyl-4-(5-phosphono-2-furanyl)oxazole 261366-75-0P, 2-Amino-5-ethyl-4-(5-phosphono-2-furanyl)oxazole 261366-76-1P, 2-Amino-5-methyl-4-(5-phosphono-2-furanyl)oxazole 261366-77-2P, 2-Amino-4-(5-phosphono-2-furanyl)oxazole 261366-78-3P, 2-Amino-5-isobutyl-4-(5-phosphono-2-furanyl)oxazole monohydrobromide 261370-26-7P 261370-27-8P, 2-Methyl-5-isobutyl-4-(5-phosphorodiamido-2-furanyl)thiazole 261370-29-0P, 2-Amino-5-methylthio-4-(5-phosphorodiamido-2-furanyl)thiazole 261370-30-3P, 2-Amino-5-isobutyl-4-(5-phosphonomonoamido-2-furanyl)thiazole 261370-31-4P, 2-Amino-5-isobutyl-4-(5-phosphorodiamido-2-furanyl)thiazole 261370-32-5P, 2-Amino-5-isobutyl-4-[5-(N,N'-diisobutylphosphorodiamido)-2-furanyl]thiazole 261370-33-6P, 2-Amino-5-isobutyl-4-[5-[N,N'-bis[(S)-1,3-bis(ethoxycarbonyl)-1-propyl]phosphorodiamido]-2-furanyl]thiazole 261370-34-7P, 2-Amino-5-isobutyl-4-[5-[N,N'-bis((S)-1-benzyloxycarbonylethyl)phosphorodiamido]-2-furanyl]thiazole 261370-35-8P 261370-39-2P, 2-Amino-5-isobutyl-4-[5-[O-phenyl-N-((S)-1-methoxycarbonylethyl)phosphonamido]-2-furanyl]thiazole 261370-44-9P, 2-Amino-5-isobutyl-4-[5-(O-phenylphosphonamido)-2-furanyl]thiazole 261370-46-1P, 2-Amino-5-isobutyl-4-(5-(O-phenyl-N-ethoxycarbonylmethylphosphonamido)-2-furanyl)thiazole 261370-48-3P, 2-Amino-5-isobutyl-4-(5-(O-phenyl-N-isobutylphosphonamido)-2-furanyl)thiazole 261370-50-7P, 2-Amino-5-isobutyl-4-[5-[O-phenyl-N-((S)-1-ethoxycarbonyl-2-phenylethyl)phosphonamido]-2-furanyl]thiazole 261370-54-1P, 2-Amino-5-isobutyl-4-[5-[O-phenyl-N-[(S)-1,3-bis(ethoxycarbonyl)propyl]phosphonamido]-2-furanyl]thiazole 261370-57-4P, 2-Amino-5-isobutyl-4-[5-[O-(3-chlorophenyl)-N-[(S)-1-(methoxycarbonyl)ethyl]phosphonamido]-2-furanyl]thiazole 261370-60-9P, 2-Amino-5-isobutyl-4-[5-[O-phenyl-N-[1,1-bis(ethoxycarbonyl)methyl]phospho namido]-2-furanyl]thiazole 261370-61-0P, 2-Amino-5-isobutyl-4-[5-[O-phenyl-N-(1-morpholinyl)phosphonamido]-2-furanyl]thiazole 261370-62-1P, 2-Amino-5-isobutyl-4-[5-[O-phenyl-N-[(S)-1-(benzyloxycarbonyl)ethyl]phosph onamido]-2-furanyl]thiazole 261370-63-2P, 2-Amino-5-isobutyl-4-(5-(O-phenyl-N-benzyloxycarbonylmethylphosphonamido)-2-furanyl)thiazole 261370-64-3P, 2-Amino-5-isobutyl-4-[5-[O-(4-methyloxyphenyl)-N-[(S)-1-(methoxycarbonyl)ethyl]phosphonamido]-2-furanyl]thiazole 261370-68-7P 261370-69-8P 261370-70-1P 261370-71-2P 261370-73-4P 261370-74-5P 261370-76-7P, 2-Amino-5-methylthio-4-(5-(N-methyl-1-phenyl-1,3-propylphosphonamido)-2-furanyl)thiazole 261370-79-0P, 2-Amino-5-isobutyl-4-[5-[[3-(3,5-dichlorophenyl)-1,3-propyl]phosphonamido]-2-furanyl]thiazole 261370-80-3P, 2-Amino-5-isobutyl-4-[5-(4,5-benzo-1-oxo-1-phospha-2-oxa-6-azacyclohexan-1-yl)-2-furanyl]thiazole 261372-35-4P, 2-Amino-4-phosphonomethyloxy-6-bromobenzothiazole 261372-36-5P, 2-Amino-4-phosphonomethyloxybenzothiazole 261372-38-7P, 2-Amino-4-phosphonomethyloxy-6-bromo-7-chlorobenzothiazole 261372-39-8P, 2-Amino-4-phosphonomethoxy-6-bromo-7-methylbenzothiazole 261372-40-1P, 2-Amino-4-phosphonomethoxy-7-methylbenzothiazole 261372-42-3P, 2-Amino-4-phosphonomethoxy-7-chlorobenzothiazole 261372-64-9P, 2-Amino-7-ethyl-6-thiocyano-4-phosphonomethoxybenzothiazole 261373-40-4P, 2-Methyl-5-ethyl-4-(5-phosphono-2-furanyl)thiazole 280779-70-6P, 2-Phenyl-5-isobutyl-4-(5-phosphono-2-furanyl)thiazole 280779-71-7P, 2-Amino-5-isopropyl-4-(5-phosphono-2-furanyl)thiazole 280779-72-8P, 2-Amino-5-methanesulfinyl-4-(5-phosphono-2-furanyl)thiazole 280779-74-0P, 2-Amino-5-(4-morpholinyl)methyl-4-(5-phosphono-2-furanyl)thiazole dihydrobromide 280779-79-5P, 2-Amino-5-ethyl-4-(5-phosphono-2-furanyl)selenazole 280779-91-1P, 2-Vinyl-5-isobutyl-4-(5-phosphono-2-furanyl)thiazole 280782-95-8P, 2-Amino-5-isobutyl-4-[5-[N,N'-bis(benzyloxycarbonylmethyl)phosphonodiamido]furanyl]-2-thiazole 280782-96-9P, 2-Amino-5-isobutyl-4-[5-[N,N'-bis[(R)-1-(methoxycarbonyl)ethyl]phosphonodiamido]furanyl]-2-thiazole 280782-97-0P, 2-Amino-5-isobutyl-4-[5-[N,N'-bis[(S)-1-(ethoxycarbonyl)ethyl]phosphonodiamido]furanyl]-2-thiazole 280782-98-1P, 2-Amino-5-isobutyl-4-[5-[N,N'-bis[(tert-butoxycarbonyl)methyl]phosphonodia mido]furanyl]-2-thiazole 280782-99-2P, 2-Amino-5-isobutyl-4-[5-[N,N'-bis[(ethoxycarbonyl)methyl]phosphonodiamido]furanyl]-2-thiazole

280783-00-8P, 2-Amino-5-isobutyl-4-[5-[N,N'-bis[(1-methyl-1-ethoxycarbonyl)ethyl]phosphonodiamido]furanyl]-2-thiazole 280783-01-9P, 2-Amino-5-isobutyl-4-[5-[N,N'-bis(ethoxycarbonylmethyl)-N,N'-dimethylphosphonodiamido]-2-furanyl]thiazole 280783-02-0P, 2-Amino-5-isobutyl-4-[5-[N,N'-bis((S)-1-benzyloxycarbonyl-2-methylpropyl]phosphonodiamido]-2-furanyl]thiazole 280783-03-1P, 2-Amino-5-isobutyl-4-[5-[[N,N'-bis((S)-1-methoxycarbonyl-3-methyl)butyl]phosphonodiamido]-2-furanyl]thiazole 280783-04-2P, 2-Amino-5-isobutyl-4-[5-[N,N'-bis[(R)-1-ethoxycarbonyl-2-(benzylthio)ethyl]phosphonodiamido]-2-furanyl]thiazole 280783-06-4P, 2-Amino-5-propylthio-4-[5-[N,N'-bis[(S)-1-(ethoxycarbonyl)ethyl]phosphonodiamido]-2-furanyl]thiazole 280783-07-5P, 2-Amino-5-isobutyl-4-[5-[N,N'-bis[(S)-1-benzyloxycarbonyl-2-methylisobutyl]phosphonodiamido]-2-furanyl]thiazole 280783-08-6P, 2-Amino-5-isobutyl-4-[5-[N,N'-bis[(S)-1-ethoxycarbonyl-3-methylbutyl]phosphonodiamido]-2-furanyl]thiazole 280783-09-7P, 2-Amino-5-isobutyl-4-[5-[N,N'-bis[(S)-1-ethoxycarbonyl-2-methylpropyl]phosphonodiamido]-2-furanyl]thiazole 280783-10-0P, 2-Amino-5-isobutyl-4-[5-[N,N'-bis[(S)-1-ethoxycarbonyl-2-phenylethyl]phosphonodiamido]-2-furanyl]thiazole 280783-11-1P, 2-Amino-5-propylthio-4-[5-[N,N'-bis[(1-methyl-1-ethoxycarbonylethyl]phosphonodiamido]-2-furanyl]]thiazole 280783-12-2P, 2-Amino-5-methylthio-4-[5-[N,N'-bis[1-methyl-1-ethoxycarbonylethyl]phosphonodiamido]-2-furanyl]thiazole 280783-13-3P, 2-Amino-5-isobutyl-4-[5-[N-morpholino-N'-[1-methyl-1-ethoxycarbonylethyl]phosphonodiamido]-2-furanyl]thiazole 280783-14-4P, 2-Amino-5-isobutyl-4-[5-[N-pyrrolidino-N'-[1-methyl-1-ethoxycarbonylethyl]phosphonodiamido]-2-furanyl]thiazole 347870-21-7P, 2-Amino-5-isobutyl-4-[5-[N,N'-bis((S)-1-ethoxycarbonylpropyl)phosphorodiamido]-2-furanyl]thiazole 347870-33-1P, 2-Amino-5-(2-thienyl)-4-(5-diethylphosphono-2-furanyl)thiazole 358670-36-7P, (5-(3,5-Dinitrophenyl)-2-furanyl)phosphonic acid 358670-37-8P, (5-(2-Amino-3,5-dinitrophenyl)-2-furanyl)phosphonic acid 358670-38-9P, (5-(5-Chloro-2-methoxyphenyl)-2-furanyl)phosphonic acid 358670-39-0P, (5-(2,5-Dichlorophenyl)-2-furanyl)phosphonic acid 358670-40-3P, (5-(2-Methylsulfamoyl-5-(trifluoromethyl)phenyl)-2-furanyl)phosphonic acid 358670-41-4P, (5-(5-Chloro-2-(methylsulfamoyl)phenyl)-2-furanyl)phosphonic acid 358670-42-5P, (5-(2-(Methylsulfamoyl)phenyl)-2-furanyl)phosphonic acid 358670-44-7P, (5-(2-Hydroxyphenyl)-2-furanyl)phosphonic acid 358670-45-8P, (5-(3,5-Dimethylphenyl)-2-furanyl)phosphonic acid 358670-46-9P, (5-(3-Bromophenyl)-2-furanyl)phosphonic acid 358670-47-0P, (5-(4-Aminophenyl)-2-furanyl)phosphonic acid 358670-48-1P, (5-(4-Chloro-2,5-dimethoxyphenyl)-2-furanyl)phosphonic acid 358670-49-2P, (5-(2-((4-Chlorobenzyl)carbamoyl)phenyl)-2-furanyl)phosphonic acid 358670-50-5P, (5-(2-((2-(4-Chlorophenyl)ethyl)carbamoyl)phenyl)-2-furanyl)phosphonic acid 358670-51-6P, (5-(2-(Benzylsulfamoyl)phenyl)-2-furanyl)phosphonic acid 358670-52-7P, (5-(2-Sulfamoylphenyl)-2-furanyl)phosphonic acid 358670-53-8P, (5-Pentamethylphenyl-2-furanyl)phosphonic acid 358670-54-9P, (5-(2,3-Dicarboethoxyphenyl)-2-furanyl)phosphonic acid 358670-56-1P, (5-(4-Acetylamino-3-methylphenyl)-2-furanyl)phosphonic acid 358670-58-3P, (5-(2,4-Dichloro-6-methylphenyl)-2-furanyl)phosphonic acid 358670-59-4P, (5-(4-Hydroxy-2-carbomethoxyphenyl)-2-furanyl)phosphonic acid 358670-60-7P, (5-(2-Carbamoyl-4-methylphenyl)-2-furanyl)phosphonic acid 358670-61-8P, (5-(2-Ethoxycarbonyl-4-hydroxyphenyl)-2-furanyl)phosphonic acid 358670-62-9P, (5-(4-Nitrophenyl)-2-furanyl)phosphonic acid 358670-63-0P, (5-(2-((2,4-Difluorophenyl)carbamoyl)phenyl)-2-furanyl)phosphonic acid 358670-64-1P, (5-(3,5-Dichlorophenyl)-2-furanyl)phosphonic acid 358670-65-2P, (5-(3-Hydroxyphenyl)-2-furanyl)phosphonic acid 358670-66-3P, (5-(5-Bromo-3-carboxyphenyl)-2-furanyl)phosphonic acid 358670-67-4P, (5-(5-Formyl-2,3-dimethoxyphenyl)-2-furanyl)phosphonic acid 358670-68-5P, (5-(2-Nitrophenyl)-2-furanyl)phosphonic acid 358670-69-6P, (5-(Biphenyl-2-yl)-2-furanyl)phosphonic acid 358670-70-9P, (5-(2-(Carboethoxy)phenyl)-2-furanyl)phosphonic acid 358670-71-0P, (5-(4-Bromophenyl)-2-furanyl)phosphonic acid 358670-72-1P, (5-(3-Propanoylphenyl)-2-furanyl)phosphonic acid 358670-73-2P,

(5-(5-Cyano-2-methoxyphenyl)-2-furanyl)phosphonic acid 358670-74-3P, (5-(2-Ethylphenyl)-2-furanyl)phosphonic acid 358670-75-4P, (5-(6-Methyl-2-nitrophenyl)-2-furanyl)phosphonic acid 358670-76-5P, (5-(4-(Acetylamino)phenyl)-2-furanyl)phosphonic acid 358670-77-6P, (5-(2,3,4,5-Tetramethylphenyl)-2-furanyl)phosphonic acid 358670-78-7P, (5-(Biphenyl-3-yl)-2-furanyl)phosphonic acid 358670-79-8P, (5-(5-Chloro-2-sulfamoylphenyl)-2-furanyl)phosphonic acid 358670-80-1P, (5-(4-(((1-Pyrrolidinyl)acetyl)amino)phenyl)-2-furanyl)phosphonic acid 358670-81-2P, (5-(3,4-Dimethylphenyl)-2-furanyl)phosphonic acid 358670-82-3P, (5-(2,4-Dinitrophenyl)-2-furanyl)phosphonic acid 358670-83-4P, (5-(3-(Aminomethyl)phenyl)-2-furanyl)phosphonic acid 358670-84-5P, (5-(4-Amino-3-fluorophenyl)-2-furanyl)phosphonic acid 358670-85-6P, (5-(3-(Hydroxymethyl)phenyl)-2-furanyl)phosphonic acid 358670-86-7P, (5-(2-Bromophenyl)-2-furanyl)phosphonic acid 358670-87-8P, (5-(2-(2-Hydroxyethyl)phenyl)-2-furanyl)phosphonic acid 358670-88-9P, (5-(4-Carbamoylphenyl)-2-furanyl)phosphonic acid 358670-89-0P, (5-(4-Cyanophenyl)-2-furanyl)phosphonic acid 358670-90-3P, (5-(3-Cyanophenyl)-2-furanyl)phosphonic acid 358670-91-4P, (5-(2-Cyanophenyl)-2-furanyl)phosphonic acid 358670-92-5P, (5-(4-Amino-3-nitrophenyl)-2-furanyl)phosphonic acid 358670-93-6P, (5-(2-Isopropylphenyl)-2-furanyl)phosphonic acid 358670-94-7P, (5-(6-Amino-2-chloro-3-pyridyl)-2-furanyl)phosphonic acid 358670-95-8P, (5-(2-Amino-5-chlorophenyl)-2-furanyl)phosphonic acid 358670-96-9P, (5-(3-Chloro-5-fluorophenyl)-2-furanyl)phosphonic acid 358670-97-0P, (5-(2-Methyl-5-nitrophenyl)-2-furanyl)phosphonic acid 358670-98-1P, (5-(5-Fluoro-3-nitrophenyl)-2-furanyl)phosphonic acid 358670-99-2P, (5-(2-Amino-5-carbomethoxyphenyl)-2-furanyl)phosphonic acid 358671-00-8P, (5-(2-Methoxy-5-nitrophenyl)-2-furanyl)phosphonic acid 358671-01-9P, (5-(2-Chloro-5-(trifluoromethyl)phenyl)-2-furanyl)phosphonic acid 358671-02-0P, (5-(2,5-Bis(trifluoromethyl)phenyl)-2-furanyl)phosphonic acid 358671-03-1P, (5-(4-Fluorophenyl)-2-furanyl)phosphonic acid 358671-04-2P, (5-(2,4-Dichlorophenyl)-2-furanyl)phosphonic acid 358671-05-3P, (5-(3-Amino-5-carbomethoxyphenyl)-2-furanyl)phosphonic acid 358671-06-4P, (5-(3-Amino-4-bromophenyl)-2-furanyl)phosphonic acid 358672-11-4P, (5-(4-Methyl-3-thienyl)-2-furanyl)phosphonic acid 389057-32-3P, (5-(2-(Propylsulfamoyl)phenyl)-2-furanyl)phosphonic acid 389057-53-8P 389057-54-9P, 2-Amino-5-ethylthiocarbonyl-4-(5-phosphono-2-furanyl)thiazole 389057-55-0P, 2-Amino-5-methylthio-4-(5-phosphono-2-furanyl)thiazole N,N-dicyclohexylammonium salt 389057-73-2P, 2-Amino-5-isobutyl-4-[5-[O-(4-chlorophenyl)-N-((S)-1-methoxycarbonylethyl)phosphonamido]-2-furanyl]thiazole 389057-74-3P, 2-Amino-5-isobutyl-4-[5-[O-phenyl-N-[2-(ethoxycarbonyl)propyl]phosphonamido]-2-furanyl]thiazole 389057-76-5P, 2-Amino-4-[[3-(3,5-dichlorophenyl)propane-1,3-diyl]phosphonomethoxy]-6,7,8,9-tetrahydronaphtho[1,2-d]thiazole
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT 213124-93-7 213199-10-1 213247-37-1 240434-61-1 280783-15-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT 213190-65-9, Exendin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(exendin and exendin agonists, insulin secretagogue; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT 9004-10-8, Insulin, biological studies 116094-23-6, Insulin aspart 133107-64-9, Insulin lispro 160337-95-1, Insulin glargine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(in combination with phosphonate or phosphorodiamidate FBPase inhibitors useful for treatment of diabetes)

IT 9001-39-2, Glucose-6-phosphatase 9001-42-7, α-Glucosidase 9001-52-9, Fructose bisphosphatase 9035-74-9, Glycogen phosphorylase **54249-88-6, Dipeptidyl peptidase-IV**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT 64-77-7, Tolbutamide 94-20-2, Chlorpropamide **114-86-3, Phenformin** 451-71-8, Glyhexamide **657-24-9, Metformin** 664-95-9, Tolcyclamide **692-13-7, Buformin** 968-81-0, Acetohexamide 1156-19-0, Tolazamide 3149-00-6, Phenbutamide 10238-21-8, Glyburide 21187-98-4, Gliclazide 25046-79-1, Glisoxepid 26944-48-9, Glibornuride 29094-61-9, Glipizide 33342-05-1, Gliquidone 56180-94-0, Acarbose 72432-03-2, Miglitol 83480-29-9, Voglibose 93479-97-1, Glimepiride 105816-04-4, Nateglinide 135062-02-1, Repaglinide 145375-43-5, Mitiglinide 161748-40-9, BTS-67582 204656-20-2, NN 2211 247016-69-9, NVP-DPP728 251572-86-8, P 32/98
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(insulin secretagogue; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT 261373-15-3P, 2-Methyl-5-isobutyl-4-(5-phosphono-2-furanyl)thiazole
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(intermediate; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT 1738-68-7, Benzyl aminoacetate 358672-65-8, 6-Amino-2-chloro-3-bromopyridine
RL: RCT (Reactant); RACT (Reactant or reagent)
(intermediate; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT 36366-55-9P, Diethyl 2-furanylphosphonate 78072-59-0P, 2-(4-Methyl-1-oxopentyl)furan 82619-14-5P, Ethoxycarbonyloxymethyl iodide 104208-14-2P 213124-94-8P, 5-Diethylphosphono-2-furaldehyde 261372-78-5P, 2-Bromo-5-isobutyl-4-(5-diethylphosphono-2-furanyl)thiazole 261373-31-3P, 2-Diethylphosphonomethyloxy-5-bromonitrobenzene 389057-77-6P, 4-Phosphonomethoxy-6,7,8,9-tetrahydronaphtho[1,2-d]thiazole dichloridate
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT 953-18-4P, (R)-Ethyl 2-amino-3-(benzylthio)propanoate 2666-93-5P, L-Leucine methyl ester 2743-60-4P, L-Leucine ethyl ester 3081-24-1P, L-Phenylalanine ethyl ester 13200-60-7P, N-Methylglycine ethyl ester 17431-03-7P, L-Valine ethyl ester 21760-98-5P, L-Valine benzyl ester 154092-64-5P, (S)-Benzyl 2-amino-3,3-dimethylbutanoate
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(reactant; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)

IT 78-81-9, Isobutylamine 88-67-5, 2-Iodobenzoic acid 98-01-1, 2-Furaldehyde, reactions 109-80-8, 1,3-Propanedithiol 110-00-9, Furan 110-70-3, N,N'-Dimethylethylenediamine 354-37-0, Trifluoroacetamidine 431-03-8, 2,3-Butanedione 459-73-4, Glycine ethyl ester 533-58-4, 2-Iodophenol 540-37-4, 4-Iodoaniline 583-55-1, 2-Bromo-1-iodobenzene 589-87-7, 1-Bromo-4-iodobenzene 591-18-4, 1-Bromo-3-iodobenzene 609-73-4, 1-Iodo-2-nitrobenzene 622-50-4, 4-Iodoacetanilide 623-00-7, 4-Bromobenzonitrile 626-02-8, 3-Iodophenol 636-98-6, 1-Iodo-4-nitrobenzene 646-07-1, 4-Methylpentanoic acid 672-57-1, 2-Chloro-1-iodo-5-trifluoromethylbenzene 696-40-2, 3-Iodobenzylamine

709-49-9, 1-Iodo-2,4-dinitrobenzene 814-49-3, Diethyl chlorophosphate
873-38-1, 2-Bromo-4-chloroaniline 875-51-4, 4-Bromo-2-nitroaniline
1074-16-4, 2-Bromophenethyl alcohol 1113-49-1, Ethyl
2-amino-2-methylpropanoate 1115-59-9, L-Alanine ethyl ester
hydrochloride 1459-01-4, 2-Iodoisopropylbenzene 1765-93-1,
4-Fluorophenylboronic acid 1817-73-8, 2-Bromo-4,6-dinitroaniline
2042-37-7, 2-Bromobenzonitrile 2113-51-1, 2-Iodobiphenyl 2113-57-7,
3-Bromobiphenyl 2491-20-5, L-Alanine methyl ester hydrochloride
3032-81-3, 3,5-Dichloroiodobenzene 3082-75-5, L-Alanine ethyl ester
3819-88-3, 3-Nitro-5-fluoro-1-iodobenzene 3853-91-6,
1-Iodo-2,3,4,5,6-pentamethylbenzene 3956-07-8, 4-Iodobenzamide
5197-28-4, 2-Bromo-4-nitroanisole 5464-79-9, 2-Amino-4-
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1-Bromo-2,5-bis(trifluoromethyl)benzene 7745-93-9, 2-Bromo-4-
nitrotoluene 13529-27-6, 2-Furaldehyde diethyl acetal 16450-41-2,
L-Glutamic acid diethyl ester 17831-01-5, L-Alanine benzyl ester
18282-40-1, 1-Ethyl-2-iodobenzene 19718-49-1, 2-Iodo-4-
carbomethoxyaniline 19829-31-3, 3'-Bromopropiophenone 21705-13-5,
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30318-99-1, 3-Bromo-4-methylthiophene 31599-61-8, 3,4-
Dimethyliodobenzene 33863-76-2, 1-Bromo-3-chloro-5-fluorobenzene
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54509-71-6, 2,3,4,5-Tetramethyliodobenzene 57455-06-8, 3-Iodobenzyl
alcohol 57772-57-3, 5-Hydroxy-2-iodobenzoic acid 63980-69-8,
1-(2-Methoxy-5-chlorophenyl)thiourea 68716-47-2, 2,4-
Dichlorophenylboronic acid 85006-23-1, 3-Aminophenylboronic acid
hydrochloride 90064-46-3, 2,5-Dimethoxy-4-iodochlorobenzene
106938-62-9, Diethylphosphonomethyl trifluoromethylsulfonate
117324-09-1, 4-Iodo-2-methylacetanilide 117572-79-9,
3-Bromo-4-methoxybenzonitrile 118486-94-5, 2-Tributylstannylfuran
125259-03-2, N-Methyl-2-iodobenzenesulfonamide 175277-97-1,
3,5-Dichloro-2-iodotoluene 188815-32-9, 3-Bromo-5-iodobenzoic acid
261369-11-3, 2-Amino-5-isobutyl-4-(5-diphenylphosphono-2-furanyl)thiazole
261372-76-3, 2-Amino-5-isobutyl-4-(5-diethylphosphono-2-furanyl)thiazole
261372-77-4, 2-Amino-5-bromo-4-(5-diethylphosphono-2-furanyl)thiazole
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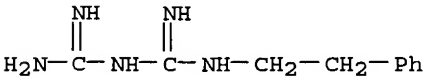
N-(4-Iodophenyl)-2-(tetrahydro-1H-pyrrol-1-yl)acetamide 271796-28-2,
4-Chloro-2-iodobenzenesulfonamide 271796-61-3, N-Benzyl-2-
iodobenzenesulfonamide 271796-68-0, N-Propyl-4-chloro-2-
iodobenzenesulfonamide 273208-13-2, N-Methyl-2-iodo-4-
(trifluoromethyl)benzenesulfonamide 273208-16-5, N-Methyl-4-chloro-2-
iodobenzenesulfonamide 304644-56-2, N-(4-Chlorobenzyl)-2-iodobenzamide
309253-36-9, 2-Iodo-5-methylbenzamide 347869-08-3, 5-Diethylphosphono-2-
(2-bromo-4-methyl-1-oxopentyl)furan 347869-10-7, 5-Diethylphosphono-2-
(bromoacetyl)furan 347869-19-6, Diethyl (5-iodo-2-furanyl)phosphonate
349110-34-5, N-(2,4-Difluorophenyl)-2-iodobenzamide 358672-63-6,
N-(4-Chlorophenethyl)-2-iodobenzamide 358672-64-7, Methyl
5-hydroxy-2-iodobenzoate 380430-56-8, 3-Amino-5-
carbomethoxyphenylboronic acid 389057-75-4, 2-Amino-4-phosphonomethoxy-
6,7,8,9-tetrahydronaphtho[1,2-d]thiazole 389057-78-7,
4-Diphenylphosphonomethoxy-6,7,8,9-tetrahydronaphtho[1,2-d]thiazole
389057-79-8, 4-Phenylphosphonomethoxy-6,7,8,9-tetrahydronaphtho-[1,2-
d]thiazole 389057-80-1, 4-Phosphonomethoxy-6,7,8,9-tetrahydronaphtho[1,2-
d]thiazole
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; combination of phosphonate or phosphorodiamidate FBPase
inhibitors and antidiabetic agents useful for treatment of diabetes)

IT **54249-88-6, Dipeptidyl peptidase-IV**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; combination of phosphonate or phosphorodiamidate FBPase
inhibitors and antidiabetic agents useful for treatment of diabetes)

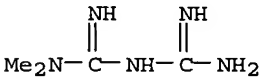
RN 54249-88-6 HCAPLUS

CN Peptidase, dipeptidyl, IV (9CI) (CA INDEX NAME)

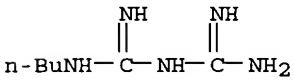
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **114-86-3, Phenformin 657-24-9,**
Metformin 692-13-7, Buformin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(insulin secretagogue; combination of phosphonate or phosphorodiamidate FBPase inhibitors and antidiabetic agents useful for treatment of diabetes)
RN 114-86-3 HCAPLUS
CN Imidodicarbonimidic diamide, N-(2-phenylethyl)- (9CI) (CA INDEX NAME)



RN 657-24-9 HCAPLUS
CN Imidodicarbonimidic diamide, N,N-dimethyl- (9CI) (CA INDEX NAME)



RN 692-13-7 HCAPLUS
CN Imidodicarbonimidic diamide, N-butyl- (9CI) (CA INDEX NAME)



L140 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2001:935405** HCAPLUS
DN 136:48456
ED Entered STN: 28 Dec 2001
TI Combinations of depeptidyl peptidase IV inhibitors and other **antidiabetic** agents for the treatment of diabetes mellitus
IN Arch, Jonathan Robert Sanders; Lenhard, James Martin
PA Smithkline Beecham PLC, UK; Smithkline Beecham Corporation
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-425
ICS A61K045-06; A61P003-06
CC 1-10 (Pharmacology)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001097808	A1	20011227	WO 2001-GB2696	20010619 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

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     BR 2001011800       A     20030527    BR 2001-11800          20010619 <--
     JP 2003535898       T2    20031202    JP 2002-503292         20010619 <--
     BG 107385           A     20030930    BG 2002-107385         20021212 <--
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     ZA 2003000203       A     20040326    ZA 2003-203            20030108 <--
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PRAI GB 2000-14969       A     20000619  <--
     WO 2001-GB2696      W     20010619  <--
CLASS
 PATENT NO.       CLASS  PATENT FAMILY CLASSIFICATION CODES
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 WO 2001097808    ICM    A61K031-425
                  ICS    A61K045-06; A61P003-06
 WO 2001097808    ECLA   A61K031/427+M; A61K045/06                    <--
 US 2003166578    NCL    514/019.000
                  ECLA   A61K031/427+M; A61K045/06                    <--
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AB A method for the treatment of diabetes mellitus, especially Type 2 diabetes and conditions associated with diabetes mellitus in a mammal, e.g. a human, comprises administering an effective, nontoxic and pharmaceutically acceptable amount of a **dipeptidyl peptidase** IV inhibitor and another **antidiabetic** agent to a mammal in need thereof.

ST depeptidyl peptidase IV inhibitor **antidiabetic** combination diabetes

IT **Antidiabetic agents**
Drug delivery systems
Drug interactions
(depeptidyl peptidase IV inhibitor combination with other **antidiabetic** agent for treatment of diabetes mellitus)

IT **Diabetes mellitus**
(**non-insulin-dependent**; depeptidyl peptidase IV inhibitor combination with other **antidiabetic** agent for treatment of diabetes mellitus)

IT **50-99-7**, D-Glucose, biological studies **54249-88-6**, **Dipeptidyl peptidase** IV 62572-11-6, Hemoglobin A1c
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(depeptidyl peptidase IV inhibitor combination with other **antidiabetic** agent for treatment of diabetes mellitus)

IT 56-03-1D, Biguanide, derivs. 64-77-7, Tolbutamide 94-20-2, Chlorpropamide **114-86-3**, **Phenformin** 339-43-5, Carbutamide 631-27-6, Glyclopyramide **657-24-9**, **Metformin** 664-95-9, Glycyclamide **692-13-7**, **Buformin** 968-81-0, Acetohexamide 1156-19-0, Tolazamide 2295-31-0D, Thiazolidinedione, derivs. 10238-21-8, Glibenclamide 21187-98-4, Gliclazide 24477-37-0, Glisolamide 25046-79-1, Glisoxepide 26944-48-9, Glibornuride 29094-61-9, Glipizide 32797-92-5, Glisentide 33342-05-1, Gliquidone 56180-94-0, Acarbose 72432-03-2, Miglitol 74772-77-3, Ciglitazone 80879-63-6, Emiglitate 83480-29-9, Voglibose 93479-97-1, Glimepiride 97322-87-7, Troglitazone 105816-04-4, Nateglinide 109229-58-5, Englitazone 111025-46-8, Pioglitazone 111025-46-8D, Pioglitazone, derivs. 122320-73-4 122320-73-4D, derivs. 135062-02-1, Repaglinide 136259-20-6 171092-64-1 177931-21-4 247016-69-9 251571-80-9
RL: PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(depeptidyl peptidase IV inhibitor combination with other **antidiabetic** agent for treatment of diabetes mellitus)

IT 9001-42-7, α-Glucosidase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; depeptidyl peptidase IV inhibitor combination with other **antidiabetic** agent for treatment of diabetes mellitus)

IT 9004-10-8, Insulin, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(secretagogues and sensitizers; depeptidyl peptidase IV inhibitor combination with other **antidiabetic** agent for treatment of diabetes mellitus)

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD

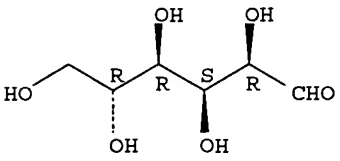
RE

(1) Beecham Group Plc; EP 0306228 A 1989 HCAPLUS
(2) Ciba Geigy Ag; WO 9819998 A 1998 HCAPLUS
(3) Deacon, C; DIABETES 1998, V47(5), P764 HCAPLUS
(4) Glund, K; WO 9961431 A 1999 HCAPLUS
(5) Holmes, D; WO 0152825 A 2001 HCAPLUS
(6) Holst, J; DIABETES 1998, V47, P1663 HCAPLUS
(7) Pauly, R; METABOLISM, CLINICAL AND EXPERIMENTAL 1999, V48(3), P385 HCAPLUS

IT **50-99-7**, D-Glucose, biological studies **54249-88-6**, **Dipeptidyl peptidase** IV
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(depeptidyl peptidase IV inhibitor combination with other **antidiabetic** agent for treatment of diabetes mellitus)

RN 50-99-7 HCAPLUS
CN D-Glucose (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.

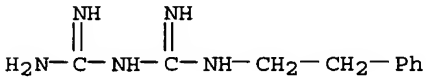


RN 54249-88-6 HCAPLUS
CN Peptidase, dipeptidyl, IV (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **114-86-3**, **Phenformin** **657-24-9**, **Metformin** **692-13-7**, **Buformin**
RL: PAC (Pharmacological activity); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(depeptidyl peptidase IV inhibitor combination with other **antidiabetic** agent for treatment of diabetes mellitus)

RN 114-86-3 HCAPLUS
CN Imidodicarbonimidic diamide, N-(2-phenylethyl)- (9CI) (CA INDEX NAME)



RN 657-24-9 HCAPLUS
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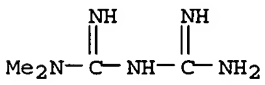

RN 692-13-7 HCAPLUS
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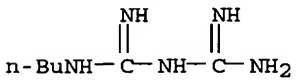

L140 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:545464 HCAPLUS
DN 135:127207
ED Entered STN: 27 Jul 2001
TI Combinations comprising dipeptidylpeptidase-IV inhibitor
IN Balkan, Boerk; Hughes, Thomas Edward; Holmes, David Grenville; Villhauer, Edwin Bernard
PA Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-00
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001052825	A2	20010726	WO 2001-EP590	20010119 <--
WO 2001052825	A3	20020328		
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PRAI US 2000-489234	A	20000121 <--		
US 2000-619262	A	20000719 <--		
WO 2001-EP590	W	20010119 <--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2001052825	ICM	A61K031-00
WO 2001052825	ECLA	A61K031/00+M; A61K031/4025+M; A61K031/44+M; A61K031/505+M; A61K045/06 <--
US 2003139434	NCL	514/275.000
	ECLA	A61K031/4025+M; A61K031/44+M; A61K031/505+M; A61K045/06 <--

OS MARPAT 135:127207
AB The invention relates to a combination which comprises a DPP-IV inhibitor and at least one further antidiabetic compound, preferably selected from the group consisting of insulin signalling pathway modulators, like inhibitors of protein tyrosine phosphatases (PTPases), non-small mol. mimetic compds. and inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT), compds. influencing a dysregulated hepatic glucose production, like inhibitors of glucose-6-phosphatase (G6Pase), inhibitors of fructose-1,6-bisphosphatase (F-1,6-BPase), inhibitors of glycogen phosphorylase (GP), glucagon receptor antagonists and inhibitors of phosphoenolpyruvate carboxykinase (PEPCK), pyruvate dehydrogenase kinase (PDHK) inhibitors, insulin sensitivity enhancers, insulin secretion enhancers, α-glucosidase inhibitors, inhibitors of gastric emptying, insulin, and

α2-adrenergic antagonists, for simultaneous, sep. or sequential use in the prevention, delay of progression or treatment of conditions mediated by dipeptidylpeptidase - IV (**DPP-IV**), in particular diabetes, more especially type 2 diabetes mellitus, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity and osteoporosis; and the use of such combination for the cosmetic treatment of a mammal in order to effect a cosmetically beneficial loss of body weight Tablets were prepared containing nateglinide.

ST dipeptidylpeptidase IV inhibitor pharmaceutical; **antidiabetic** dipeptidylpeptidase IV inhibitor pharmaceutical

IT **Antidiabetic agents**
Antiobesity agents
Drug delivery systems
Gastric emptying
(combinations comprising dipeptidylpeptidase-IV inhibitor)

IT Adrenoceptor antagonists
(α2-; combinations comprising dipeptidylpeptidase-IV inhibitor)

IT 64-77-7, Tolbutamide 94-20-2, Chloropropamide 339-43-5, Carbutamide 451-71-8, Glyhexamide **657-24-9**, **Metformin** 664-95-9, Tolcyclamide 673-06-3D, D-Phenylalanine, derivs. 968-81-0, Acetohexamide 1156-19-0, Tolazamide 3149-00-6, Phenbutamide 7440-62-2D, Vanadium, compds., biological studies 10238-21-8, Glibenclamide 21187-98-4, Gliclazide 25046-79-1, Glisoxepid 26944-48-9, Glibornuride 29094-61-9, Glipizide 33342-05-1, Gliquidone 93479-97-1, Glimepiride 97322-87-7, Troglitazone 105816-04-4, Nateglinide 111025-46-8, Pioglitazone 122320-73-4, Rosiglitazone 135062-02-1, Repaglinide 247016-69-9 274901-16-5
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(combinations comprising dipeptidylpeptidase-IV inhibitor)

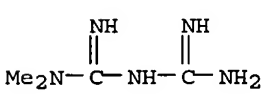
IT **50-99-7**, Glucose, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hepatic production; combinations comprising dipeptidylpeptidase-IV inhibitor)

IT 9001-39-2, Glucose 6-phosphatase 9001-42-7, α-Glucosidase 9001-52-9, Fructose 1,6-bisphosphatase 9030-45-9, Glutamine fructose 6-phosphate amidotransferase 9035-74-9, Glycogen phosphorylase 9074-01-5, Pyruvate dehydrogenase kinase 37341-55-2, Phosphoenolpyruvate carboxykinase **54249-88-6**, dipeptidylpeptidase-IV 79747-53-8
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; combinations comprising dipeptidylpeptidase-IV inhibitor)

IT 9004-10-8, Insulin, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sensitivity enhancers; combinations comprising dipeptidylpeptidase-IV inhibitor)

IT **657-24-9**, **Metformin**
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(combinations comprising dipeptidylpeptidase-IV inhibitor)

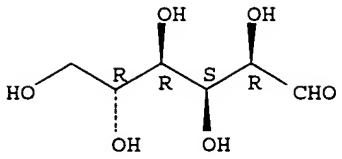
RN 657-24-9 HCAPLUS
CN Imidodicarbonimidic diamide, N,N-dimethyl- (9CI) (CA INDEX NAME)



IT **50-99-7**, Glucose, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hepatic production; combinations comprising dipeptidylpeptidase-IV inhibitor)

RN 50-99-7 HCAPLUS
CN D-Glucose (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 54249-88-6, dipeptidylpeptidase-IV
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; combinations comprising dipeptidylpeptidase-IV inhibitor)
RN 54249-88-6 HCAPLUS
CN Peptidase, dipeptidyl, IV (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L140 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:101689 HCAPLUS
DN 132:132142
ED Entered STN: 13 Feb 2000
TI Reversal of increased lymphocyte PC-1 activity in patients with Type 2 diabetes treated with **metformin**
AU Stefanovic, Vladisav; Antic, Slobodan; Mitic-Zlatkovic, Marina; Vlahovic, Predrag
CS Institute of Nephrology and Hemodialysis, Faculty of Medicine, Nis, 18000, Yugoslavia
SO Diabetes/Metabolism Research and Reviews (1999), 15(6), 400-404
CODEN: DMRRFM; ISSN: 1520-7552
PB John Wiley & Sons Ltd.
DT Journal
LA English
CC 1-10 (Pharmacology)
AB The plasma cell differentiation antigen (PC-1) is an inhibitor of insulin receptor tyrosine kinase activity, and has been implicated in the pathogenesis of insulin resistance in Type 2 diabetes. **Metformin** increases peripheral insulin sensitivity and, therefore, we have studied the effect of **metformin** treatment on lymphocyte PC-1 (ecto-alkaline phosphodiesterase I, APD) in patients with Type 2 diabetes. Basal, Con A (Con A)-, and phorbol-12-myristate-13-acetate (PMA)-stimulated lymphocyte PC-1, aminopeptidase N (APN), and **dipeptidyl-peptidase** IV (**DPP IV**) activities were determined in 16 patients with Type 2 diabetes before and after 3 mo of **metformin** treatment. Lymphocyte PC-1 in patients with Type 2 diabetes was increased significantly ($p<0.001$) over control; however, **metformin** treatment brought its activity in unstimulated and Con A-stimulated lymphocytes to the control level. PMA-stimulated PC-1 in patients with Type 2 diabetes was 17-times higher than in controls, and was reduced to near the control level by 3-mo **metformin** treatment. In Type 2 diabetes, PMA-stimulated ecto-**DPP IV** was significantly ($p<0.005$) increased over control, but was reduced after **metformin** treatment. This study has shown an increased activity of lymphocyte PC-1 in Type 2 diabetes and its reversal by 3-mo **metformin** treatment, corresponding to the improvement of insulin sensitivity. Data obtained are consistent with a role of PC-1 in insulin resistance and suggest a new mechanism of action for **metformin** via PC-1 inhibition.
ST **metformin** diabetes mellitus lymphocyte PC1 antigen
IT **Diabetes mellitus**
(**non-insulin-dependent**; reversal of increased lymphocyte PC-1 activity in patients with type 2 diabetes treated with **metformin**)
IT Antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(plasma cell differentiation, lymphocyte; reversal of increased lymphocyte PC-1 activity in patients with type 2 diabetes treated with **metformin**)

IT **Antidiabetic agents**
Obesity
(reversal of increased lymphocyte PC-1 activity in patients with type 2 diabetes treated with **metformin**)
IT **50-99-7**, D-Glucose, biological studies
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(**blood**; reversal of increased lymphocyte PC-1 activity in patients with type 2 diabetes treated with **metformin**)
IT **657-24-9**, **Metformin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU** (**Therapeutic use**); BIOL (Biological study); USES (Uses)
(reversal of increased lymphocyte PC-1 activity in patients with type 2 diabetes treated with **metformin**)
IT **9032-67-1**, **Dipeptidyl-peptidase** 9054-63-1, Alanine aminopeptidase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(reversal of increased lymphocyte PC-1 activity in patients with type 2 diabetes treated with **metformin**)
RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Balkan, B; Diabetologia 1997, V40(Suppl 1), PA131
(2) DeFronzo, R; Diabetes 1988, V37, P667 MEDLINE
(3) Fery, F; Metabolism 1997, V46, P227 HCAPLUS
(4) Frittitta, L; Diabetes 1998, V47, P1095 HCAPLUS
(5) Frittitta, L; Diabetologia 1996, V39, P1190 HCAPLUS
(6) Frittitta, L; Diabetologia 1997, V40, P282 HCAPLUS
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(8) Grupe, A; J Biol Chem 1995, V270, P22085 HCAPLUS
(9) Hickman, S; J Biol Chem 1985, V260, P6098 HCAPLUS
(10) Moe, O; J Biol Chem 1983, V258, P6941 HCAPLUS
(11) National Diabetes Data Group; Diabetes 1979, V28, P1039
(12) Nolan, J; Diabetes 1997, V46, P994 HCAPLUS
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(14) Pauly, R; Regul Pept 1996, V64, P148
(15) Rebbe, N; Mol Immunol 1993, V30, P87 HCAPLUS
(16) Rebbe, N; Proc Natl Acad Sci U S A 1991, V88, P5192 HCAPLUS
(17) Schon, E; Biol Chem Hoppe Seyler 1990, V371, P699 MEDLINE
(18) Stefanovic, V; Immunology 1993, V80, P465 HCAPLUS
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(20) Stefanovic, V; Pediatr Nephrol 1998, V12, P755 MEDLINE
(21) Stefanovic, V; Ren Physiol Biochem 1995, V18, P12 HCAPLUS
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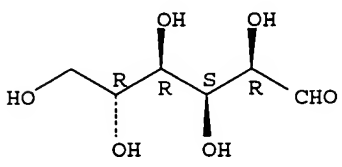
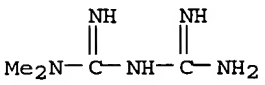
(23) Stumwoll, M; N Engl J Med 1995, V333, P550
(24) UK Prospective Diabetes Study Group; Lancet 1998, V352, P854
(25) Youngren, J; Diabetes 1996, V45, P1324 HCAPLUS
IT **50-99-7**, D-Glucose, biological studies
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(**blood**; reversal of increased lymphocyte PC-1 activity in patients with type 2 diabetes treated with **metformin**)
RN 50-99-7 HCAPLUS
CN D-Glucose (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **657-24-9, Metformin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(reversal of increased lymphocyte PC-1 activity in patients with type 2 diabetes treated with **metformin**)
RN 657-24-9 HCAPLUS
CN Imidodicarbonimidic diamide, N,N-dimethyl- (9CI) (CA INDEX NAME)



IT **9032-67-1, Dipeptidyl-peptidase**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(reversal of increased lymphocyte PC-1 activity in patients with type 2 diabetes treated with **metformin**)
RN 9032-67-1 HCAPLUS
CN Peptidase, dipeptidyl (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> b biosis
FILE 'BIOSIS' ENTERED AT 14:32:19 ON 30 NOV 2005
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 23 November 2005 (20051123/ED)

=> d all l81 tot

L81 ANSWER 1 OF 10 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2005:519288 BIOSIS
DN PREV200510297202
TI Effects of the short-acting **dipeptidyl peptidase** IV inhibitor PSN9301 and **metformin** alone and in combination on glucose tolerance and body weight in the fa/fa Zucker rat, and in a polygenetic rat model of diabetes.
AU McCormack, J. G. [Reprint Author]; **Kuhn-Wache, K.**; Freyse, E.-J.; Berg, S.; Lykkegaard, K.; Larsen, P. J.; **Demuth, H.-U.**
CS Prosid Ltd, Oxford, UK
SO Diabetologia, (2005) Vol. 48, No. Suppl. 1, pp. A287.
Meeting Info.: 41st Annual Meeting of the European-Association-for-the-Study-of-Diabetes. Athens, GREECE. September 10 -15, 2005. European Assoc Study Diabet.
CODEN: DBTGAJ. ISSN: 0012-186X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 23 Nov 2005
Last Updated on STN: 23 Nov 2005
CC General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Carbohydrates 10068
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Metabolism - Metabolic disorders 13020

Nutrition - General studies, nutritional status and methods 13202
Nutrition - Malnutrition and obesity 13203
Digestive system - Physiology and biochemistry 14004
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Endocrine - General 17002
Endocrine - Pancreas 17008
Pharmacology - General 22002
Pharmacology - Endocrine system 22016

IT Major Concepts
Pharmacology; Nutrition; Enzymology (Biochemistry and Molecular Biophysics); Endocrine System (Chemical Coordination and Homeostasis)

IT Parts, Structures, & Systems of Organisms
blood: blood and lymphatics; pancreas: endocrine system, digestive system

IT Diseases
diabetes: endocrine disease/pancreas, metabolic disease
Diabetes Mellitus (MeSH)

IT Diseases
obesity: nutritional disease
Obesity (MeSH)

IT Chemicals & Biochemicals
glucose; **dipeptidyl peptidase** IV [EC 3.4.14.5]; insulin: secretion; HbA1c; **metformin**: antidiabetic-drug, oral administration, efficacy; PSN9301: enzyme inhibitor-drug, antidiabetic-drug, dosage, efficacy, oral administration

IT Methods & Equipment
oral glucose tolerance test: laboratory techniques

ORGN Classifier
Muridae 86375

Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia

Organism Name
Zucker rat (common): mature, male

Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 58367-01-4 (glucose)
54249-88-6 (dipeptidyl peptidase IV)
54249-88-6 (EC 3.4.14.5)
9004-10-8 (insulin)
62572-11-6 (HbA1c)
657-24-9 (metformin)

L81 ANSWER 2 OF 10 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN **2005:473909** BIOSIS
DN PREV200510274670
TI Long-term efficacy of the DPP-4 inhibitor, LAF237, in patients with type 2 diabetes inadequately treated with **metformin**.
AU Pratley, R. E. [Reprint Author]; Gomis, R.; Standl, E.; Schweizer, A.; Mills, D.; Ahren, B.
CS Novartis Pharmaceut, CD and MA, E Hanover, NJ USA
SO Diabetologia, (AUG 2004) Vol. 47, No. Suppl. 1, pp. A69-A70.
Meeting Info.: 40th Annual Meeting of the European-Association-for-the-Study-of-Diabetes. Munich, GERMANY. September 05 -09, 2004. European Assoc Study Diabetes.
CODEN: DBTGAJ. ISSN: 0012-186X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 16 Nov 2005
Last Updated on STN: 16 Nov 2005
CC General biology - Symposia, transactions and proceedings 00520
Clinical biochemistry - General methods and applications 10006

Biochemistry studies - General 10060
Pathology - General 12502
Pathology - Therapy 12512
Metabolism - General metabolism and metabolic pathways 13002
Metabolism - Metabolic disorders 13020
Endocrine - General 17002
Endocrine - Pancreas 17008
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Pharmacology - Endocrine system 22016
IT Major Concepts
Pharmacology; Clinical Chemistry (Allied Medical Sciences); Metabolism; Clinical Endocrinology (Human Medicine, Medical Sciences)
IT Diseases
type 2 diabetes: endocrine disease/pancreas, metabolic disease, drug therapy, pathology
Diabetes Mellitus, Non-Insulin-Dependent (MeSH)
IT Chemicals & Biochemicals
incretin; GLP-1 [glucagon-like peptide-1]; GIP [glucose-dependent insulinotropic peptide]; DPP-4 [**dipeptidyl peptidase** IV] [**EC 3.4.14.5**]:
inhibition; **metformin**: antidiabetic-drug, tolerance, efficacy, oral administration, dosage; LAF237: enzyme inhibitor-drug, antidiabetic-drug, tolerance, efficacy, oral administration, dosage
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common): female, male
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 54241-84-8 (incretin)
657-24-9 (**metformin**)

L81 ANSWER 3 OF 10 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN **2004:365799** BIOSIS
DN PREV200400369126
TI **Metformin** causes reduction of food intake and body weight gain and improvement of glucose intolerance in combination with **dipeptidyl peptidase** IV inhibitor in Zucker fa/fa rats.
AU Yasuda, Nobuyuki [Reprint Author]; Inoue, Takashi; Nagakura, Tadashi; Yamazaki, Kazuto; Kira, Kazunobu; Saeki, Takao; Tanaka, Isao
CS Tsukuba Res Labs, Eisai Co Ltd, 5-1-3 Tokodai, Tsukuba, Ibaraki, 3002635, Japan
n-yasuda@hhc.eisai.co.jp
SO Journal of Pharmacology and Experimental Therapeutics, (August 2004) Vol. 310, No. 2, pp. 614-619. print.
ISSN: 0022-3565 (ISSN print).
DT Article
LA English
ED Entered STN: 8 Sep 2004
Last Updated on STN: 8 Sep 2004
AB An incretin hormone, glucagon-like peptide-1 (GLP-1), has been shown to lower plasma glucose via glucose-dependent insulin secretion and to reduce appetite. We previously found that the biguanide **metformin**, an antidiabetic agent, causes a significant increase of plasma active GLP-1 level in the presence of **dipeptidyl peptidase** IV (**DPPIV**) inhibitor in normal rats. This finding suggested that the combination treatment might produce a greater antidiabetic and anorectic effect, based on enhanced GLP-1 action. In this study, we assessed the effects of subchronic treatment with **metformin** and a **DPPIV** inhibitor, valine-pyrrolidide (val-pyr), on glycemic control, food intake, and weight gain using Zucker fa/fa rats, a model of obesity and impaired glucose tolerance. The combination treatment caused a significant increase of GLP-1 level in Zucker fa/fa rats. In a

subchronic study, val-pyr, **metformin**, or both compounds were administered orally b.i.d. for 14 days. The combination treatment significantly decreased food intake and body weight gain, although neither **metformin** nor val-pyr treatment alone had any effect. In an oral glucose tolerance test on day 1, the coadministration caused a greater improvement of glucose tolerance and a prominent increase of plasma active GLP-1 without marked insulin secretion. The 14-day combination treatment produced a potent reduction of fasting blood glucose and plasma insulin levels. These results demonstrate that the combination therapy of **metformin** with **DPPIV** inhibitor leads to reduced food intake and body weight gain, most likely through the significant increase of plasma GLP-1 level. The combination therapy seems to be a good candidate for treatment of type 2 diabetes with obesity.

CC Behavioral biology - General and comparative behavior 07002
Behavioral biology - Animal behavior 07003
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Carbohydrates 10068
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Diagnostic 12504
Pathology - Therapy 12512
Metabolism - General metabolism and metabolic pathways 13002
Metabolism - Metabolic disorders 13020
Nutrition - General studies, nutritional status and methods 13202
Nutrition - Malnutrition and obesity 13203
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Endocrine - General 17002
Endocrine - Pancreas 17008
Pharmacology - General 22002
Pharmacology - Endocrine system 22016

IT Major Concepts
Behavior; Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Metabolism; Nutrition; Pharmacology

IT Parts, Structures, & Systems of Organisms
plasma: blood and lymphatics

IT Diseases
obesity: nutritional disease
Obesity (MeSH)

IT Diseases
type 2 diabetes mellitus: endocrine disease/pancreas, metabolic disease, diagnosis, drug therapy, therapy
Diabetes Mellitus, Non-Insulin-Dependent (MeSH)

IT Chemicals & Biochemicals
dipeptidyl peptidase IV [**EC 3.4.14.5**]: activity, inhibition; glucagon-like peptide-1 [GLP-1]; glucose: intolerance, tolerance; insulin: secretion; **metformin**: antidiabetic-drug, oral administration; valine-pyrrolidide: enzyme inhibitor-drug

IT Miscellaneous Descriptors
appetite; body weight gain; food intake; glycemic control

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Zucker rat (common)
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN **54249-88-6 (dipeptidyl peptidase IV)**
54249-88-6 (EC 3.4.14.5)
89750-14-1 (glucagon-like peptide-1)
89750-14-1 (GLP-1)

50-99-7Q (glucose)
58367-01-4Q (glucose)
9004-10-8 (insulin)
657-24-9 (metformin)

L81 ANSWER 4 OF 10 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN **2004:266672** BIOSIS
DN PREV200400268176
TI The combination of **metformin** and a **dipeptidyl peptidase** IV inhibitor prevents 5-fluorouracil-induced reduction of small intestine weight.
AU Yamazaki, Kazuto [Reprint Author]; Yasuda, Nobuyuki; Inoue, Takashi; Nagakura, Tadashi; Kira, Kazunobu; Saeki, Takao; Tanaka, Isao
CS Tsukuba Res Labs, Eisai & Co Ltd, 5-1-3 Tokodai, Tsukuba, Ibaraki, 3002635, Japan
k5-yamazaki@hhc.eisai.co.jp
SO European Journal of Pharmacology, (March 19 2004) Vol. 488, No. 1-3, pp. 213-218. print.
ISSN: 0014-2999 (ISSN print).
DT Article
LA English
ED Entered STN: 26 May 2004
Last Updated on STN: 26 May 2004
AB Glucagon-like peptide 2 (GLP-2), which has intestinotrophic effects, is secreted from L-cells in the intestine in response to nutrient ingestion and is degraded by **dipeptidyl peptidase** IV (**DPPIV**). In this report, we show that biguanides promote GLP-2 release. Plasma GLP-2 levels were significantly increased by 1.4- to 1.6-fold in fasted F344 rats 1 h after oral meformin (300 mg/kg), **phenformin** (30 and 100 mg/ kg) and **buformin** (100 mg/ka) treatment. In addition, **metformin** administration (300 mg/kg, p.o.) significantly elevated plasma GLP-2 in fasted CD-1 mice by about 2.0-fold 1 and 3 h after the treatment. **Metformin** and/or valine-pyrrolidide, a **DPPIV** inhibitor, was orally given (300 and 30 mg/kg, respectively, p.o., b.i.d., 3 days) to BALB/c mice treated with 5-fluorouracil (5-FU; 60 mg/kg, s.i.d.), which induces gastrointestinal damage leading to a reduction of small intestine wet weight. **Metformin** and valine-pyrrolidide co-administration prevented the 5-FU-induced reduction of wet weight of the small intestine, whereas **metformin** or valine-pyrrolidide alone had no effect. These results suggest that GLP-2 is co-secreted with GLP-1 flollowing biguanide stimulation, and that the combination of **metformin** with a **DPPIV** inhibitor might a useful oral treatment for gastrointestinal damage, based on GLP-2 actions. Copyright 2004 Elsevier B.V. All rights reserved.
CC Biochemistry studies - General 10060
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Digestive system - Physiology and biochemistry 14004
IT Major Concepts
Biochemistry and Molecular Biophysics; Digestive System (Ingestion and Assimilation)
IT Parts, Structures, & Systems of Organisms
L-cells; small intestine: digestive system, weight
IT Chemicals & Biochemicals
5-fluorouracil; **buformin**; **dipeptidyl peptidase** IV inhibitor; glucagon-like peptide 2 [GLP-2]; meformin; **metformin**; **phenformin**
IT Miscellaneous Descriptors
nutrient ingestion
RN 51-21-8 (5-fluorouracil)
692-13-7 (buformin)
89750-15-2 (glucagon-like peptide 2)
89750-15-2 (GLP-2)
657-24-9 (metformin)
114-86-3 (phenformin)

L81 ANSWER 5 OF 10 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN **2003:531063** BIOSIS
DN PREV200300531255
TI Synergistic effects of a combination of **DPPIV** inhibitor with **metformin** on glycemic control, food intake and weight gain in Zucker fa/fa rats.
AU Yasuda, N. [Reprint Author]; Inoue, T. [Reprint Author]; Nagakura, T. [Reprint Author]; Yamazaki, K. [Reprint Author]; Kira, K. [Reprint Author]; Saeki, T. [Reprint Author]; Tanaka, I. [Reprint Author]
CS Tsukuba Research Labs III, Eisai Co., Ltd., Tsukuba, Japan
SO Diabetologia, (August 2003) Vol. 46, No. Supplement 2, pp. A 284. print.
Meeting Info.: 18th Congress of the International Diabetes Federation. Paris, France. August 24-29, 2003. International Diabetes Federation.
CODEN: DBTGAJ. ISSN: 0012-186X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 12 Nov 2003
Last Updated on STN: 12 Nov 2003
CC General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Carbohydrates 10068
Pathology - Therapy 12512
Metabolism - General metabolism and metabolic pathways 13002
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Pharmacology - General 22002
Pharmacology - Endocrine system 22016
IT Major Concepts
Metabolism; Pharmacology
IT Parts, Structures, & Systems of Organisms
plasma: blood and lymphatics
IT Chemicals & Biochemicals
dipeptidyl peptidase IV [DPPIV]; glucagon-like peptide-1 [GLP-1]; glucose; insulin; **metformin**: antidiabetic-drug; valine-pyrrolidide: antidiabetic-drug, enzyme inhibitor-drug
IT Miscellaneous Descriptors
body weight; drug synergy; food intake; insulin sensitivity
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
rat (common): Zucker fa/fa
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN **54249-88-6** (**dipeptidyl peptidase** IV)
54249-88-6 (**DPPIV**)
89750-14-1 (glucagon-like peptide-1)
89750-14-1 (GLP-1)
50-99-7Q (glucose)
58367-01-4Q (glucose)
9004-10-8 (insulin)
657-24-9 (**metformin**)

L81 ANSWER 6 OF 10 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2002:503242 BIOSIS
DN PREV200200503242
TI Rebuttal to Deacon and Holst: "**Metformin** effects on **dipeptidyl peptidase** IV degradation of glucagon-like peptide-1" versus "**Dipeptidyl peptidase** inhibition as an approach to the treatment and prevention of type 2 diabetes: A historical perspective".

AU **Demuth, Hans-Ulrich** [Reprint author]; Hinke, Simon A.; Pederson, Raymond A.; McIntosh, Christopher H. S.
CS Biocenter, **Probiodrug** AG, Weinbergweg 22, D-06120, Halle (Saale), Germany
hans-ulrich.demuth@probiodrug.de
SO Biochemical and Biophysical Research Communications, (August 16, 2002) Vol. 296, No. 2, pp. 229-232. print.
CODEN: BBRCA9. ISSN: 0006-291X.
DT Article
LA English
ED Entered STN: 25 Sep 2002
Last Updated on STN: 25 Sep 2002
CC Biochemistry studies - General 10060
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Metabolism - General metabolism and metabolic pathways 13002
Metabolism - Metabolic disorders 13020
Endocrine - General 17002
Endocrine - Pancreas 17008
Pharmacology - General 22002
Pharmacology - Endocrine system 22016
IT Major Concepts
Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Metabolism; Pharmacology
IT Diseases
type 2 diabetes mellitus: endocrine disease/pancreas, metabolic disease, drug therapy, prevention and control
Diabetes Mellitus, Non-Insulin-Dependent (MeSH)
IT Chemicals & Biochemicals
dipeptidyl peptidase IV; glucagon-like peptide-1;
metformin: antidiabetic-drug, pharmacodynamics
IT Methods & Equipment
Dipeptidyl peptidase inhibition-based therapy: therapeutic method
ORGN Classifier
Animalia 33000
Super Taxa
Animalia
Organism Name
animal
Taxa Notes
Animals
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse: animal model
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN **54249-88-6** (**dipeptidyl peptidase** IV)
657-24-9 (**metformin**)

L81 ANSWER 7 OF 10 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN **2002:384358** BIOSIS
DN PREV200200384358
TI **Dipeptidyl peptidase** IV inhibition as an approach to the treatment and prevention of type 2 diabetes: A historical perspective.
AU Deacon, Carolyn F. [Reprint author]; Holst, Jens J.
CS Department of Medical Physiology, Panum Institute, Blegdamsvej 3, DK-2200, Copenhagen N, Denmark
deacon@mfi.ku.dk
SO Biochemical and Biophysical Research Communications, (May 31, 2002) Vol. 294, No. 1, pp. 1-4. print.
CODEN: BBRCA9. ISSN: 0006-291X.

DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 10 Jul 2002
Last Updated on STN: 10 Jul 2002
CC Biochemistry studies - General 10060
Pathology - Therapy 12512
Metabolism - General metabolism and metabolic pathways 13002
Metabolism - Metabolic disorders 13020
Endocrine - General 17002
Endocrine - Pancreas 17008
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Pharmacology - Endocrine system 22016
IT Major Concepts
Clinical Endocrinology (Human Medicine, Medical Sciences); Pharmacology
IT Diseases
type 2 diabetes: endocrine disease/pancreas, metabolic disease, prevention and control, therapy
Diabetes Mellitus, Non-Insulin-Dependent (MeSH)
IT Chemicals & Biochemicals
dipeptidyl peptidase IV: inhibition; glucagon-like peptide-1: antidiabetic-drug; incretin hormone: metabolism; **metformin**: antidiabetic-drug
IT Miscellaneous Descriptors
historical perspective
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human: patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN **54249-88-6** (**dipeptidyl peptidase** IV)
657-24-9 (**metformin**)

L81 ANSWER 8 OF 10 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2002:245928 BIOSIS
DN PREV200200245928
TI **Metformin** effects on dipeptidylpeptidase IV degradation of glucagon-like peptide-1.
AU Hinke, Simon A.; Kuehn-Wache, Kerstin; **Hoffmann, Torsten**; Pederson, Raymond A.; McIntosh, Christopher H. S.; **Demuth, Hans-Ulrich** [Reprint author]
CS Biocenter, **Probiodrug** Research, Weinbergweg 22, D-06120, Halle (Saale), Germany
Hans-Ulrich.Demuth@probiodrug.de
SO Biochemical and Biophysical Research Communications, (March 15, 2002) Vol. 291, No. 5, pp. 1302-1308. print.
CODEN: BBRCA9. ISSN: 0006-291X.
DT Article
LA English
ED Entered STN: 17 Apr 2002
Last Updated on STN: 17 Apr 2002
AB There is current interest in the use of inhibitors of **dipeptidyl peptidase** IV (DP IV) as therapeutic agents to normalize glycemic excursions in type 2 diabetic patients. Data indicating that **metformin** increases the circulating amount of active glucagon-like peptide-1 (GLP-1) in obese nondiabetic subjects have recently been presented, and it was proposed that **metformin** might act as a DP IV inhibitor. This possibility has been investigated directly using a number of in vitro methods. Studies were performed on DP IV enzyme from three sources: 20% human serum, purified porcine kidney DP IV, and recombinant human DP IV. Inhibition of DP IV hydrolysis of the substrate Gly-Pro-pNA by **metformin** was examined spectrophotometrically.

Effects of **metformin** on GLP-1(7-36NH2) degradation were assessed by mass spectrometry. In addition, surface plasmon resonance was used to establish whether or not **metformin** had any effect on GLP-1(7-36NH2) or GLP-1(9-36NH2) interaction with immobilized porcine or human DP IV. **Metformin** failed to alter the kinetics of Gly-Pro-pNA hydrolysis or GLP-1 degradation tested according to established methods. Surface plasmon resonance recordings indicated that both GLP-1(7-36NH2) and GLP-1(9-36NH2) show micromolar affinity (KD) for DP IV, but neither interaction was influenced by **metformin.** The results conclusively indicate that **metformin** does not act directly on DP IV, therefore alternative explanations for the purported effect of **metformin** on circulating active GLP-1 concentrations must be considered.

CC Biochemistry studies - General 10060
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Metabolism - Metabolic disorders 13020
Endocrine - Pancreas 17008
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Pharmacology - Endocrine system 22016

IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Pharmacology

IT Diseases
type 2 diabetes: endocrine disease/pancreas, metabolic disease
Diabetes Mellitus, Non-Insulin-Dependent (MeSH)

IT Chemicals & Biochemicals
dipeptidylpeptidase IV [**EC 3.4.14.5**]; glucagon-like peptide-1; **metformin**: antidiabetic-drug

IT Methods & Equipment
matrix-assisted laser-desorption ionization-time of flight mass spectrometry: analytical method; spectrophotometry: analytical method, photometry; surface plasmon resonance: analytical method

IT Miscellaneous Descriptors
enzyme-substrate interaction

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
Suidae 85740
Super Taxa
Artiodactyla; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
porcine
Taxa Notes
Animals, Artiodactyls, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates

RN **54249-88-6** (dipeptidylpeptidase IV)
54249-88-6 (EC 3.4.14.5)
657-24-9 (metformin)

L81 ANSWER 9 OF 10 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2001:448982 BIOSIS
DN PREV200100448982
TI Investigation of **metformin** effects on DPIV-mediated GLP-1 degradation.
AU Hinke, Simon A.; **Hoffmann, Torsten; Kuhn-Wache, Kerstin; Bar, Joachim**; Manhart, Susanne; Wermann, Michael; Pederson, Raymond A.; McIntosh, Christopher H. S.; **Demuth, Hans-Ulrich**

SO Diabetes, (June, 2001) Vol. 50, No. Supplement 2, pp. A311-A312. print.
Meeting Info.: 61st Scientific Sessions of the American Diabetes Association. Philadelphia, Pennsylvania, USA. June 22-26, 2001. American Diabetes Association.
CODEN: DIAEAZ. ISSN: 0012-1797.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 19 Sep 2001
Last Updated on STN: 22 Feb 2002
CC General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - General and comparative studies: coenzymes 10802
Pathology - Therapy 12512
Endocrine - General 17002
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Endocrine System (Chemical Coordination and Homeostasis); Pharmacology
IT Parts, Structures, & Systems of Organisms
kidney: excretory system; serum: blood and lymphatics
IT Chemicals & Biochemicals
GLP-1 [glucagon-like peptide-1]: amino terminal, degradation kinetics, incretin hormone, insulinotropic peptide, mediation, regulation; dipeptidylpeptidase IV [DPIV]: inhibition; incretin; insulin; **metformin**: antidiabetic-drug, enzyme inhibitor-drug, dose, insulin sensitizing biguanide
IT Methods & Equipment
Gly-Pro-4-nitroanilide colorimetry: analytical method; surface plasmon resonance: analytical method
IT Miscellaneous Descriptors
protein-protein interaction; weak enzyme inhibition; Meeting Poster; Meeting Abstract
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
ORGN Classifier
Suidae 85740
Super Taxa
Artiodactyla; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
pig
Taxa Notes
Animals, Artiodactyls, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates
RN **54249-88-6** (dipeptidylpeptidase IV)
54249-88-6 (DPIV)
54241-84-8 (incretin)
9004-10-8 (insulin)
657-24-9 (**metformin**)

L81 ANSWER 10 OF 10 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN **2000:118379** BIOSIS
DN PREV200000118379
TI Reversal of increased lymphocyte PC-1 activity in patients with type 2 diabetes treated with **metformin.**
AU Stefanovic, Vladisav [Reprint author]; Antic, Slobodan; Mitic-Zlatkovic,

Marina; Vlahovic, Predrag
CS Institute of Nephrology and Hemodialysis, B. Taskovic 48, 18000, Nis, Yugoslavia
SO Diabetes-Metabolism Research and Reviews, (Nov.-Dec., 1999) Vol. 15, No. 6, pp. 400-404. print.
ISSN: 1520-7552.
DT Article
LA English
ED Entered STN: 29 Mar 2000
Last Updated on STN: 3 Jan 2002
AB Background The plasma cell differentiation antigen (PC-1) is an inhibitor of insulin receptor tyrosine kinase activity, and has been implicated in the pathogenesis of insulin resistance in Type 2 diabetes. **Metformin** increases peripheral insulin sensitivity and, therefore, we have studied the effect of **metformin** treatment on lymphocyte PC-1 (ecto-alkaline phosphodiesterase I, APD) in patients with Type 2 diabetes. Methods Basal, concanavalin A (Con A)-, and phorbol-12-myristate-13-acetate (PMA)-stimulated lymphocyte PC-1, aminopeptidase N (APN), and dipeptidylpeptidase IV (**DPP IV**) activities were determined in 16 patients with Type 2 diabetes before and after 3 months of **metformin** treatment. Results Lymphocyte PC-1 in patients with Type 2 diabetes was increased significantly ($p < 0.001$) over control; however, **metformin** treatment brought its activity in unstimulated and Con A-stimulated lymphocytes to the control level. PMA-stimulated PC-1 in patients with Type 2 diabetes was 17-times higher than in controls, and was reduced to near the control level by 3-month **metformin** treatment. In Type 2 diabetes, PMA-stimulated ecto-**DPP IV** was significantly ($p < 0.005$) increased over control, but was reduced after **metformin** treatment. Conclusion This study has shown an increased activity of lymphocyte PC-1 in Type 2 diabetes and its reversal by 3-month **metformin** treatment, corresponding to the improvement of insulin sensitivity. Data obtained are consistent with a role of PC-1 in insulin resistance and suggest a new mechanism of action for **metformin** via PC-1 inhibition.
CC Biochemistry studies - Proteins, peptides and amino acids 10064
Pathology - Therapy 12512
Metabolism - Metabolic disorders 13020
Blood - Blood and lymph studies 15002
Endocrine - Pancreas 17008
Pharmacology - Clinical pharmacology 22005
Pharmacology - Endocrine system 22016
Immunology - General and methods 34502
Immunology - Immunopathology, tissue immunology 34508
IT Major Concepts
Clinical Endocrinology (Human Medicine, Medical Sciences); Clinical Immunology (Human Medicine, Medical Sciences); Metabolism; Pharmacology
IT Parts, Structures, & Systems of Organisms
lymphocyte: blood and lymphatics, immune system
IT Diseases
insulin resistance: endocrine disease/pancreas, immune system disease
Insulin Resistance (MeSH)
IT Diseases
type 2 diabetes mellitus: endocrine disease/pancreas, metabolic disease
Diabetes Mellitus, Non-Insulin-Dependent (MeSH)
IT Chemicals & Biochemicals
aminopeptidase N; dipeptidylpeptidase IV; insulin: sensitivity; **metformin**: antidiabetic-drug; plasma cell differentiation antigen [PC-1]
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human: patient
Taxa Notes

Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 9054-63-1 (aminopeptidase N)
54249-88-6 (dipeptidylpeptidase IV)
9004-10-8 (insulin)
657-24-9 (**metformin**)

=> => b medl
FILE 'MEDLINE' ENTERED AT 14:42:30 ON 30 NOV 2005

FILE LAST UPDATED: 29 NOV 2005 (20051129/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow promt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all l146 tot

L146 ANSWER 1 OF 3 MEDLINE on STN
AN **2005134214** MEDLINE
DN PubMed ID: 15765627
TI Harnessing the therapeutic potential of glucagon-like peptide-1: a critical review.
AU Baggio Laurie L; Drucker Daniel J
CS Department of Medicine, University of Toronto, Toronto, Ontario, Canada.
SO Treat Endocrinol, (2002) 1 (2) 117-25. Ref: 136
Journal code: 101132977. ISSN: 1175-6349.
CY New Zealand
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 200504
ED Entered STN: 20050316
Last Updated on STN: 20050407
Entered Medline: 20050406
AB Glucagon-like peptide-1 (GLP-1) is synthesized from proglucagon in enteroendocrine cells and regulates glucose homeostasis via multiple complementary actions on appetite, gastrointestinal motility and islet hormone secretion. GLP-1 is secreted from the distal gut in response to food ingestion, and levels of circulating GLP-1 may be diminished in patients with type 2 diabetes mellitus. GLP-1 administration stimulates glucose-dependent insulin secretion, inhibits glucagon secretion, and lowers blood glucose in normal and diabetic rodents and in humans. GLP-1 exerts additional glucose-lowering actions in patients with diabetes mellitus already treated with **metformin** or sulfonylurea therapy. GLP-1 inhibits gastric emptying in healthy individuals and those with diabetes mellitus, and excess GLP-1 administration may cause nausea or vomiting in susceptible individuals. Chronic GLP-1 treatment of normal or diabetic rodents is associated with bodyweight loss and GLP-1 agonists transiently inhibit food intake and may prevent bodyweight gain in humans. The potential for GLP-1 therapy to prevent deterioration of beta-cell function is exemplified by studies demonstrating that GLP-1 analogs stimulate proliferation and neogenesis of beta-cells, leading to expansion

of beta-cell mass in diabetic rodents. The rapid N-terminal inactivation of bioactive GLP-1 by **dipeptidyl peptidase**-IV (**DPP-IV**) limits the utility of the native peptide for the treatment of patients with diabetes mellitus, and has fostered the development of more potent and stable protease-resistant GLP-1 analogs which exhibit longer durations of action. The importance of **DPP -IV** for glucose control is illustrated by the phenotype of rodents with genetic inactivation of **DPP-IV** which exhibit reduced glycemic excursion and increased levels of circulating GLP-1 in vivo. Inhibitors of **DPP-IV** potentiate incretin action by preventing degradation of GLP-1 and glucose-dependent insulinotropic peptide, and lower blood glucose in normal rodents and in experimental models of diabetes mellitus. Hence, orally available **DPP-IV** inhibitors also represent a new class of therapeutic agents that enhance incretin action for the treatment of patients with type 2 diabetes mellitus.

CT *Diabetes Mellitus, Type 2: DT, drug therapy
*Diabetes Mellitus, Type 2: ME, metabolism
*Glucagon: ME, metabolism
*Glucagon: TU, therapeutic use
Humans
*Peptide Fragments: ME, metabolism
*Peptide Fragments: TU, therapeutic use
*Protein Precursors: ME, metabolism
*Protein Precursors: TU, therapeutic use
Research Support, Non-U.S. Gov't

RN 89750-14-1 (glucagon-like peptide 1); 9007-92-5 (Glucagon)

CN 0 (Peptide Fragments); 0 (Protein Precursors)

L146 ANSWER 2 OF 3 MEDLINE on STN

AN **2004355566** MEDLINE

DN PubMed ID: 15039452

TI **Metformin** causes reduction of food intake and body weight gain and improvement of glucose intolerance in combination with **dipeptidyl peptidase** IV inhibitor in Zucker fa/fa rats.

AU Yasuda Nobuyuki; Inoue Takashi; Nagakura Tadashi; Yamazaki Kazuto; Kira Kazunobu; Saeki Takao; Tanaka Isao

CS Tsukuba Research Laboratories, Eisai Co., Ltd., Tokodai, Tsukuba, Ibaraki, Japan.. n-yasuda@hhc.eisai.co.jp

SO Journal of pharmacology and experimental therapeutics, (2004 Aug) 310 (2) 614-9. Electronic Publication: 2004-03-23.
Journal code: 0376362. ISSN: 0022-3565.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200503

ED Entered STN: 20040720
Last Updated on STN: 20050329
Entered Medline: 20050328

AB An incretin hormone, glucagon-like peptide-1 (GLP-1), has been shown to lower plasma glucose via glucose-dependent insulin secretion and to reduce appetite. We previously found that the biguanide **metformin**, an antidiabetic agent, causes a significant increase of plasma active GLP-1 level in the presence of **dipeptidyl peptidase** IV (**DPPIV**) inhibitor in normal rats. This finding suggested that the combination treatment might produce a greater antidiabetic and anorectic effect, based on enhanced GLP-1 action. In this study, we assessed the effects of subchronic treatment with **metformin** and a **DPPIV** inhibitor, valine-pyrrolidide (val-pyr), on glycemic control, food intake, and weight gain using Zucker fa/fa rats, a model of obesity and impaired glucose tolerance. The combination treatment caused a significant increase of GLP-1 level in Zucker fa/fa rats. In a subchronic study, val-pyr, **metformin**, or both compounds were administered orally b.i.d. for 14 days. The combination treatment significantly decreased food intake and body weight gain, although neither

metformin nor val-pyr treatment alone had any effect. In an oral glucose tolerance test on day 1, the coadministration caused a greater improvement of glucose tolerance and a prominent increase of plasma active GLP-1 without marked insulin secretion. The 14-day combination treatment produced a potent reduction of fasting blood glucose and plasma insulin levels. These results demonstrate that the combination therapy of **metformin** with **DPPIV** inhibitor leads to reduced food intake and body weight gain, most likely through the significant increase of plasma GLP-1 level. The combination therapy seems to be a good candidate for treatment of type 2 diabetes with obesity.

CT Check Tags: Comparative Study; Male
Animals
***Antigens, CD26: ME, metabolism**
Drug Therapy, Combination
*Eating: DE, drug effects
Eating: PH, physiology
*Glucose Intolerance: BL, blood
Glucose Intolerance: DT, drug therapy
Glucose Intolerance: EN, enzymology
***Metformin: PD, pharmacology**
Metformin: TU, therapeutic use
Protease Inhibitors: PD, pharmacology
Protease Inhibitors: TU, therapeutic use
Rats
Rats, Zucker
*Weight Gain: DE, drug effects
Weight Gain: PH, physiology

RN **657-24-9 (Metformin)**

CN 0 (Protease Inhibitors); **EC 3.4.14**
.5 (Antigens, CD26)

L146 ANSWER 3 OF 3 MEDLINE on STN

AN **2002396080** MEDLINE

DN PubMed ID: 12145269

TI On combination therapy of diabetes with **metformin** and **dipeptidyl peptidase** IV inhibitors.

CM Comment on: Diabetes Care. 2001 Mar;24(3):489-94. PubMed ID: 11289473

AU Hinke Simon A; McIntosh Christopher H S; Hoffmann Torsten; Kuhn-Wache Kerstin; Wagner Leona; Bar Joachim; Manhart Susanne; Wermann Michael; Pederson Raymond A; Demuth Hans-Ulrich

SO Diabetes care, (2002 Aug) 25 (8) 1490-1; author reply 1491-2.
Journal code: 7805975. ISSN: 0149-5992.

CY United States

DT Commentary
Letter

LA English

FS Priority Journals

EM 200301

ED Entered STN: 20020730
Last Updated on STN: 20030115
Entered Medline: 20030113

CT ***Antigens, CD26**
*Diabetes Mellitus, Type 2: DT, drug therapy
Drug Therapy, Combination
*Glucagon: TU, therapeutic use
Humans
*Hypoglycemic Agents: TU, therapeutic use
***Metformin: TU, therapeutic use**
*Peptide Fragments: TU, therapeutic use
*Protein Precursors: TU, therapeutic use

RN **657-24-9 (Metformin)**; 89750-14-1 (glucagon-like peptide 1); 9007-92-5 (Glucagon)

CN 0 (Hypoglycemic Agents); 0 (Peptide Fragments); 0 (Protein Precursors); **EC 3.4.14.5** (Antigens, CD26)

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=> d his

     (FILE 'HOME' ENTERED AT 12:41:01 ON 30 NOV 2005)

     FILE 'HCAPLUS' ENTERED AT 12:41:40 ON 30 NOV 2005
L1            2 US2005176622/PN OR (US2003-667200# OR US2003-443417#)/AP,PRN

     FILE 'REGISTRY' ENTERED AT 12:42:46 ON 30 NOV 2005

     FILE 'HCAPLUS' ENTERED AT 12:42:46 ON 30 NOV 2005
L2              TRA L1 1- RN :       71 TERMS

     FILE 'REGISTRY' ENTERED AT 12:42:47 ON 30 NOV 2005
L3           71 SEA L2
                ACT GUD200BGU/A
                ---------
L4   (       2)SEA FILE=HCAPLUS ABB=ON  PLU=ON  US2005176622/PN OR (US2003-667
L5              SEL  PLU=ON  L4 1- RN :      71 TERMS
L6   (      71)SEA FILE=REGISTRY ABB=ON  PLU=ON  L5
L7   (       1)SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 AND METFORMIN?
L8   (       1)SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 AND PHENFORMIN
L9   (       1)SEA FILE=REGISTRY ABB=ON  PLU=ON  L6 AND BUFORMIN
L10          3 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L7 OR L8 OR L9)
                ---------
                ACT GUD200DPP/A
                ---------
L11        233 SEA FILE=REGISTRY ABB=ON  PLU=ON  (DIPEPTIDYL (1A)PEPTIDASE? (1
                ---------
                ACT GUD200SEQ1/A
                ---------
L12  (      16)SEA FILE=REGISTRY ABB=ON  PLU=ON  C30H54N8O12
L13  (       9)SEA FILE=REGISTRY ABB=ON  PLU=ON  L12 AND SQL=7
L14          1 SEA FILE=REGISTRY ABB=ON  PLU=ON  680594-87-0/BI AND L13
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L15          2 L3 AND DIPEPTID?

     FILE 'HCAPLUS' ENTERED AT 12:45:21 ON 30 NOV 2005
L16       2404 L11,L15
L17       4560 DIPEPTID? (1A)?PEPTIDAS? OR (E C OR EC)()(3 4 14 11 OR 3 4 14 5
               E DIPEPTID/CT
L18       2774 E29,E31,E34-35
               E E35+ALL
L19       2535 E6+OLD
L20       5075 L16-19
L21          1 L14
L22       2687 L10
L23        636 BUFORMIN# OR BUTYLBIGUANIDE OR BUTYL()(BIGUANIDE? OR DIGUANIDE?
L24       2643 DIMETHYLDIGUANIDE  OR DIMETHYLBIGUANIDE OR DIMETHYL ()(BIGUANID
L25        381 DIMETHYLGUANYLGUANIDINE OR DIMETHYL ()(GUANYLGUANIDINE OR GUANY
L26        891 GLUKOPOSTIN# OR GLYPHEN OR PEDG OR PHENETHYLDIGUANIDE OR PHENET
L27        213 PHENETHYL (2A)BIGUANIDE
L28       4214 L22-27
L29         68 L20 AND L28
               E DIABETES/CT
L30      79299 E3-58
               E E4+ALL
L31      12713 E5+OLD
               E E7+ALL
L32        228 E4
               E E6
               E E3+ALL
L33      77959 E15+OLD,NT
               E E20
L34      15099 E3-4
               E E3+ALL
```

```
L35       19345 E3+OLD,NT
                E HYPERGLYCEMIA/CT
L36        9106 E3-5
                E E3+ALL
L37       10411 E4+OLD
                E KUHN WACHE K/AU
L38           5 E4
                E KUHN W K/AU
L39          16 E3
                E BAR J/AU
                E BAR J/AU
L40          38 E3-4
                E BAER J/AU
L41          80 E3-13
                E BAER JOACHIM/AU
L42           4 E3-4
                E DEMTH H/AU
                E DEMUTH H/AU
L43         160 E3,E7-10
                E DE MUTH H/AU
                E HEISER U/AU
L44          30 E3-5
                E BRANDT W/AU
L45         381 E3-10
                E BRANDT WOLFGANG/AU
L46          84 E3-4
                E PROBIODRUG/CS,PA
L47          56 PROBIODRUG/CS,PA
                E PROSIDION/CS,PA
L48           9 PROSIDION/CS,PA
L49          64 L29 AND L30-37
L50         388 L20 (L) BIND?
L51           3 L50 AND L49
L52           6 L49,L51 AND L38-48
L53          58 L49,L51 NOT L52
L54          58 L53 AND (PY<=20030129 OR AY<=20030129 OR PRY<=20030129)
L55           1 L1 AND L22-27
L56          54 L54 AND L28 (L)THU/RL
L57           2 L56 AND L50
                SEL AN DN 1
L58           1 E1-3 AND L57
L59           3 L51,L58

     FILE 'BIOSIS' ENTERED AT 13:27:33 ON 30 NOV 2005
L60        3531 L16-17
                E DIPEPTIDY/CT
L61         109 E11-12,E20-21,E27
L62        3874 L28
L63           0 L14
L64          14 L62 AND L60-61
                E JUHN W K/AU
                E KUHN W K/AU
L65           3 E3
L66           5 E8-9
                E BAR J/AU
L67          74 E3-5,E12
                E BAER J/AU
L68         220 E3-14
L69           2 E26-27
                E DEMUTH H/AU
L70         155 E3-7
                E DE MUTH H/AU
                E HOFFMANN T/AU
L71         162 E3-9
                E HOFFMANN TORSTEN/AU
L72         101 E3-4
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                E HEISER U/AU
L73          10 E3-5
                E BRANDT W/AU
L74         175 E3-9
                E BRANDT WOLFGANG/AU
L75          29 E3-4
L76          38 (PROBIODRUG OR PROSIDION)/CS
L77           4 L64 AND L65-76
L78          10 L64 NOT L77
                SEL AN 1 3 4 5 8 10 L78
L79           6 E1-6 AND L78
L80           0 L79 AND SECOND?
L81          10 L77,L79

     FILE 'REGISTRY' ENTERED AT 13:44:31 ON 30 NOV 2005
L82           1 INSULIN/CN
L83        8231 INSULIN/CNS

     FILE 'HCAPLUS' ENTERED AT 13:45:14 ON 30 NOV 2005
L84      131285 L83
                E INSULIN/CT
L85      106355 E3-6
                E E3+ALL
L86      106850 E5+NT
                E GLUCOSE TOLERANCE/CT
                E BLOOD SUGAR/CT
                E E3+ALL
L87       16746 E1
L88       27358 E2
                E GLUCOSE/CT
L89      183031 E3
                E E3+ALL
L90      195930 E5+NT
L91         927 L28 AND L87-90
L92         457 L91 AND L28 (L)THU/RL
L93         398 L92 AND L30-37
L94         398 L93 AND (PY<=20030129 OR AY<=20030129 OR PRY<=20030129)
L95         364 L94 AND (ANTIDIABET? OR ANTI DIABET?)
L96          22 L95 AND SECONDARY
L97           1 L38-48 AND L96
L98          21 L96 NOT L97
                SEL AN 3 L98
L99           1 E1-2 AND L98
L100         20 L95 AND L20
L101          3 L100 AND L38-48
L102         17 L100 NOT L101
                SEL AN 2 15-17
L103          4 E3-10 AND L102
L104          0 L103 AND (BIND? OR SECOND?)
L105        349 L84-86 AND L20
L106        109 L84-86(L)THU/RL AND L20
L107         95 L106 AND L30-37
L108          3 L107 AND SECONDAR?
L109          1 L38-48 AND L108
L110          2 L108 NOT L109
                E SULFONYLUREAS/CT
                E SULFONYLUREA/CT
L111       1459 E3,E7
                E E7+ALL
L112       6776 E4+OLD,NT
L113         86 L112 AND L20
L114          9 L113 AND SECOND?
                E PPAR/CT
L115          0 E3-4
                E E4+ALL
                E E2+ALL
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L116        124 E1(L)AGONIST?
                E E8
L117       6527 E3-7
                E E3+ALL
L118       6692 E7+OLD,NT
L119        959 L117-118 (L) AGONIST?
L120         56 L116,L119 AND L20
L121          3 L120 AND L38-48
L122         53 L120 NOT L121
L123         53 L122 AND (PY<=20030129 OR AY<=20030129 OR PRY<=20030129)
L124          0 DIPEPTIDYLPEPTIDASE ()IV DIPEPTIDYLPEPTIDASEIV
L125        485 DIPEPTIDYLPEPTIDASE-IV
L126       5122 L20,L125
L127         56 L116,L119 AND L126
L128         53 L127 NOT L38-48
L129         53 L123,L128
L130          0 L129 AND SECONDAR?

     FILE 'REGISTRY' ENTERED AT 14:25:10 ON 30 NOV 2005
L131        786 (GLP OR GLUCAGON LIKE PEPTIDE?)/CNS

     FILE 'REGISTRY' ENTERED AT 14:25:28 ON 30 NOV 2005

     FILE 'HCAPLUS' ENTERED AT 14:26:24 ON 30 NOV 2005
L132       3123 L131
L133       3817 GLP OR GLUCAGON LIKE PEPTIDE?
L134        359 L132-133 AND L126
L135         12 L134 AND SECONDARY
L136          7 L135 NOT L38-48
L137          1 SECONDARY (L) BIND? AND L136
L138          6 L136 NOT L137
                SEL AN 3
L139          1 L138 AND E1-2
L140         11 L59,L99,L101,L103,L109,L139

     FILE 'MEDLINE' ENTERED AT 14:32:38 ON 30 NOV 2005
L141       3268 L60
                E DIPEPTIDYL/CT
                E E23+ALL
L142       1494 E2
                E E2+ALL
L143       1494 ANTIGENS, CD26/CT
L144         15 L28 AND L141-143
                SEL AN 4 8 12
L145          3 L144 AND E1-3
L146          3 L145 AND L141-145

     FILE 'EMBASE' ENTERED AT 14:42:47 ON 30 NOV 2005
L147      51034 L60
L148       9889 L28
L149        245 L124-125
L150        815 L147,L149 AND L148
L151         51 L150 AND SECONDARY
                E KUHN W K/AU
L152         10 E3,E8
                E BAR J/AU
L153        166 E3-8
                E BAER J/AU
L154        159 E3-14
                E DEMUTH H/AU
L155         93 E3-4
                E DE MUTH H/AU
                E HOFFMANN T/AU
L156        226 E3-13
                E HEISER U/AU
L157         14 E3-4
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                E BRANDT W/AU
L158          148 E3-10
L159           26 L76
L160            0 L151 AND L152-159
L161            2 L150 AND L152-159
L162           31 L151 AND PY<=2003
L163           30 L162 AND ?DIABET?

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